OPEN

Distinct Characteristics of Suspected Non-Alzheimer Pathophysiology in Relation to Cognitive Status and Cerebrovascular Burden

Min Young Chun, MD, PhD,†‡ Yu Hyun Park, PhD,*§‖ Hee Jin Kim, MD, PhD,*‖¶# Duk L. Na, MD, PhD,*‖ Jun Pyo Kim, MD, PhD,*‖ Sang Won Seo, MD, PhD,*‖¶#** and Hyemin Jang, MD, PhD*††*

Purpose of the Report: This study investigated the prevalence and clinical characteristics of suspected non-Alzheimer disease pathophysiology (SNAP) across varying cognitive statuses and cerebral small vessel disease (CSVD) burden.

Patients and Methods: We included 1992 participants with cognitive status categorized as cognitively unimpaired, mild cognitive impairment, or dementia. β-amyloid (Aβ, A) positivity was assessed by Aβ PET, and neurodegeneration (N) positivity was determined through hippocampal volume. Participants were further divided by the presence or absence of severe CSVD. The clinical and imaging characteristics of A−N+ (SNAP) group were compared with those of the A−N− and A+N+ groups.

Results: SNAP participants were older and had more vascular risk factors compared with A–N– and A+N+ in the CSVD(−) cohort. SNAP and A+N+ showed similar cortical thinning. At the dementia stage, SNAP had a cognitive trajectory similar to A+N+ in the CSVD(−) cohort. However, SNAP exhibited less cognitive decline than A+N+ in the CSVD(+) cohort.

Conclusions: SNAP is characterized by distinct clinical and imaging characteristics; however, it does not necessarily indicate a benign prognosis, particularly at the dementia stage. These findings highlight the need to assess SNAP in relation to the cognitive stage and CSVD presence to better understand its progression and guide interventions.

Key Words: suspected non-Alzheimer pathology, amyloid, neurodegeneration, cognitive impairment, cerebrovascular small vessel disease, machine learning

(*Clin Nucl Med* 2025;50:368–380)

Neurodegeneration is the key process underlying cognitive impairment and dementia. Among the different primary pathologies contributing to neurodegeneration,[1–4] Alzheimer disease (AD), characterized by β-amyloid (Aβ) deposition, is one of the most important causes.[3,5,6] The advances in the domain of neuroimaging have facilitated the detection of Aβ and neurodegeneration in vivo.[7] Consequently, the National Institute on Aging and Alzheimer's Association (NIA-AA) has introduced diagnostic criteria for AD based on the Aβ (A) and neurodegeneration (N) classification.[4,8–11] Notably, suspected non-Alzheimer disease pathophysiology (SNAP) has been described as a

Received for publication November 18, 2024; accepted January 23, 2025.

From the *Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine; †Department of Neurology, Seoul National University Hospital, Seoul National University College of Medicine; ‡Department of Neurology, Yonsei University College of Medicine; §Neuroscience Center, Samsung Medical Center; ‖Alzheimer's Disease Convergence Research Center, Samsung Medical Center; ¶Department of Health Sciences and Technology, SAIHST, Sungkyunkwan University; #Department of Digital Health, SAIHST, Sungkyunkwan University; **Department of Clinical Research Design & Evaluation, SAIHST, Sungkyunkwan University, Gangnam-gu; and ††Department of Neurology, Seoul National University Hospital, Seoul National University College of Medicine, Jongno-gu, Seoul, South Korea.

M.Y.C. and Y.H.P. contributed equally to this work as co-first authors.

H.J. and S.W.S. contributed equally to this article as co-corresponding authors.

M.C., H.J., and S.S. conceptualized and designed the study and drafted the manuscript. M.C., Y.P., and J.Y. accessed and verified the data. H.K., D.L.N., J.K., and S.S. acquired the data. Y.P. and J.K. contributed to data curation and analysis. Funding was obtained by H.J. and S.S. The manuscript was revised by S.S., and H.J. and S.S. supervised the study.

Conflicts of interest and sources of funding: This research was supported by a grant of the Korea Dementia Research Project through the Korea Dementia Research Center (KDRC), funded by the Ministry of Health & Welfare and Ministry of Science and ICT, Republic of Korea (grant number: RS-2020-KH106434 and RS-2020-KH107436); a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare and Ministry of Science and ICT, Republic of Korea (grant number: RS-2022-KH127756 and RS-2022-KH125667); Future Medicine 2030 Project of the Samsung Medical Center [#SMX1250081]; the "Korea National Institute of Health" research project (2024-ER1003-01); partly supported by Institute of Information & Communications Technology Planning & Evaluation (IITP) grant funded by the Korea government (MSIT) (No. RS-2021-II212068, Artificial Intelligence Innovation Hub); and the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (NRF-2019R1A5A2027340 and NRF-2020R1A2C1009778).

Correspondence to: Sang Won Seo, MD, PhD, Department of Neurology, Sungkyunkwan University School of Medicine, Samsung Medical Center, 81 Irwon-ro, Gangnam-gu, Seoul 06351, South Korea. E-mail: sangwonseo@empal.com; or Hyemin Jang, MD, PhD, Department of Neurology, Seoul National University Hospital, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul, Republic of Korea. E-mail: hmjang57@gmail.com.

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.nuclearmed.com.

DOI: 10.1097/RLU.0000000000005793

biomarker-based concept of positive neurodegeneration without significant Aβ deposition by the NIA-AA.[8–11]

Most previous studies[8,12] on SNAP in cognitively unimpaired (CU) participants have reported that SNAP-CU is associated with a benign clinical outcome.[4,13,14] However, compared with individuals without Aβ or neurodegeneration, individuals with SNAP-mild cognitive impairment (SNAP-MCI) exhibited poorer lower metabolic activity in the temporoparietal region, hippocampal atrophy, and cognitive deterioration.[15–20] These findings indicate the potential differences between SNAP-CU and SNAP-MCI. The characteristics of SNAP in dementia are underexplored. Some studies have suggested that SNAP may relate to non-AD pathophysiology, such as cerebral small vessel diseases (CSVD).[1,17,21] However, evidence on the prevalence of SNAP and its clinical characteristics according to the CSVD burden remains scarce. Thus, investigating the prevalence and characteristics of SNAP by cognitive status and CSVD burden can elucidate the underlying etiology of SNAP.

Aβ positron emission tomography (PET) scans and cerebrospinal fluid studies have been used widely to determine Aβ positivity (A+/A–); however, defining neurodegeneration as negative (N–) or positive (N+) remains challenging. Most previous studies established the 90th percentile of hippocampal volume (HV) residuals (calculated from the regression in the cognitively normal group) of individuals with AD dementia as the cutoff for defining neurodegeneration.[8,22–24] However, this method is critically dependent on the data distribution and structure in the CU or dementia group, limiting its broad application due to variability issues, particularly if the CU or dementia group is small. Machine-learning (ML) clustering methods, which naturally develop the cutoff in a data-driven manner, have been proposed as an alternative. These methods are less likely to deviate as they use data encompassing normal to severe neurodegeneration.

This study aimed to (1) investigate the distribution of A/N classification using an ML-derived neurodegeneration cutoff in a large memory clinic cohort according to the cognitive status and CSVD burden, and (2) explore the brain imaging and clinical characteristics of SNAP in each cognitive status and CSVD burden group. The comprehensive analysis conducted in this study could provide insights into the prevalence of SNAP, which has shown distinct associations with cognitive status and CSVD burden, as well as the possible etiologies of SNAP.

PATIENTS AND METHODS

Participants

A total of 1992 participants with CU (n = 630), MCI (n = 750), or dementia (n = 612) who visited the memory clinic at Samsung Medical Center (SMC) in Seoul, Korea, between August 2015 and December 2021, were included in this study. All participants had undergone comprehensive dementia evaluation, including a neuropsychological test [Seoul Neuropsychological Screening Battery (SNSB)];[25,26] blood tests, including apolipoprotein (*APOE*) genotyping; brain magnetic resonance imaging (MRI); and Aβ PET scans. The syndromal cognitive staging proposed by the NIA-AA Research Framework was used to classify the participants into the CU, MCI, and dementia stages.[27] The CU participants met the following criteria: (1) no medical history that is likely to affect cognitive function based on Christensen's health screening criteria[28] and (2) no objective cognitive impairment according to a comprehensive neuropsychological test battery in any cognitive domains (above −1.0 SD of age-matched and education-matched norms in the memory domain and −1.5 SD in other cognitive domains).[29] All participants with MCI exhibited objective cognitive impairment in any cognitive domain; however, no significant impairment in activities of daily living was observed.[10] The participants with dementia met the NIA-AA criteria.[11] Individuals with white matter hyperintensities (WMH) owing to etiologies other than vascular pathology, including radiation injury, leukodystrophy, demyelinating disorders (eg, multiple sclerosis), or metabolic/toxic disorders; traumatic brain injury; territorial infarction; brain tumor; or rapidly progressive dementias and treatable dementias, including conditions such as normal pressure hydrocephalus, vitamin B_{12} deficiency, and hypothyroidism, were excluded from the study. Details of Brain MRI acquisition and Aβ PET imaging acquisition are provided in the Supplementary Methods, Supplemental Digital Content 1, http://links.lww.com/CNM/A539.

This study was approved by the institutional review board of SMC. Written informed consent was obtained from the patients and caregivers.

Definitions of key abbreviations used in this study are provided in Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/CNM/A539.

WMH Visual Rating

The participants were considered to have CSVD when their WMH was classified as severe based on the WMH visual rating scale (Fig. 1A) proposed by the Clinical Research Center for Dementia, which is comparable to the Fazekas scale.[30–32] Criteria for severe WMH included: (1) deep WMH longest diameter $\geq$25 mm and (2) periventricular WMH maximum length (perpendicular or horizontal) $\geq$10 mm. To assess interrater reliability, 3 neurologists rated WMH severity on 100 randomly selected fluid-attenuated inversion recovery images, achieving excellent agreement (Fleiss $\kappa = 0.84$). Finally, 1594 participants without severe WMH were categorized as CSVD(−) and 398 with severe WMH as CSVD(+).

Measurement of Cortical Thickness and HV

The images were processed using the CIVET anatomic pipeline (version 2.1.0) (Fig. 1B).[33] The native MR images were registered to the Montreal Neurological Institute's 152 brain template via a linear transformation[34] and corrected for intensity nonuniformities using the N3 algorithm.[35] The images were separated into white matter, gray matter, cerebrospinal fluid, and background. The Marching-cubes algorithm extracted the inner and outer surfaces of the cortex to determine cortical thickness defined as the Euclidean distance between corresponding vertices.[36]

The total volume of the voxels within the skull-stripped brain mask was measured to determine the intracranial volume (ICV). The cortical thickness was measured in the native space by applying an inverse transformation matrix to the cortical surface and reconstructing them in native space, as the cortical surface models were extracted from MRI volumes transformed into stereotaxic space.[37]

Surface-based two-dimensional registration was performed using a sphere-to-sphere warping algorithm. The cortical thickness values were normalized spatially to compare the thickness of the corresponding registration

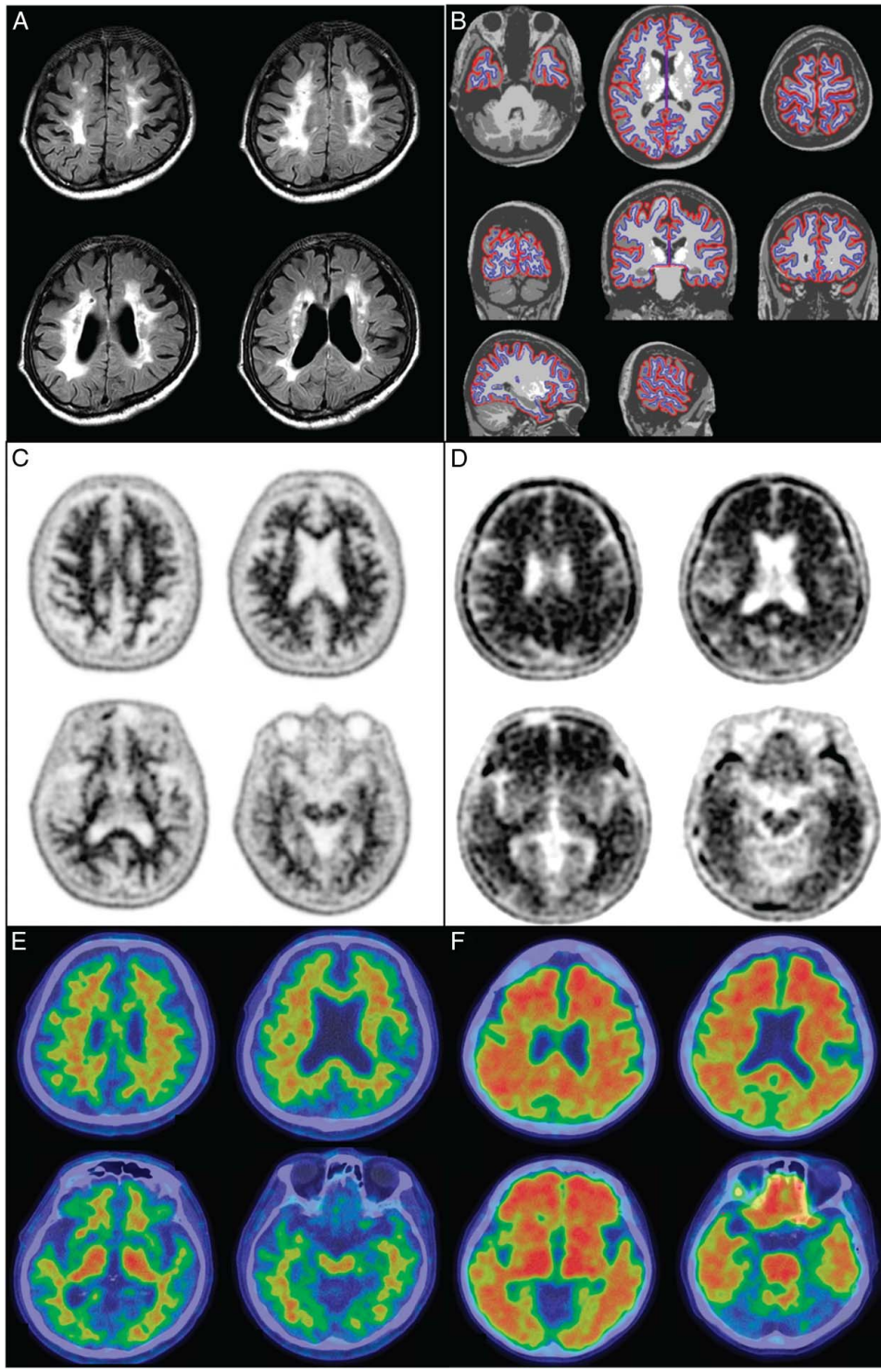

FIGURE 1. Representative imaging of white matter hyperintensity, cortical thickness, and amyloid PET scans. (A) Brain axial MR images showing severe white matter hyperintensity as classified by the visual rating scale, (B) Representative cortical thickness measurements obtained using the 3T MRI and CIVET anatomic pipeline, with regions of interest highlighted, (C) ^{18}F-florbetaben (FBB) PET scan illustrating a negative case without β-amyloid (Aβ) deposition, (D) FBB PET scan demonstrating a positive case with significant Aβ deposition, (E) ^{18}F-flutemetamol (FMM) scan showing a negative case without Aβ deposition, and (F) FMM PET scan illustrating a positive case with Aβ deposition.

algorithm with that of an unbiased iterative group template with enhanced anatomic detail[38] to transform the thickness information for the vertices into an unbiased iterative group template. Each map of cortical thickness was blurred via surface-based diffusion smoothing with a full width at half-maximum of 20 mm, to increase the signal-to-noise ratio and statistical power.[37,39]

An automated hippocampus segmentation method, which combined a graph cut algorithm with an atlas-based segmentation and morphologic opening, was used to determine HV, as previously described.[40]

ML Method for Defining the Neurodegeneration Cutoff

Adjusted HV (HVa) was used to define neurodegeneration, as described in previous studies.[8,22–24,41] Two separate datasets (Supplementary Figure 1, Supplemental Digital Content 1, http://links.lww.com/CNM/A539) were used to obtain the HVa cutoff. An independent dataset of 591 healthy participants aged ≥55 years who had undergone a health screening examination at the Health Promotion Center of SMC and had a Korean-Mini Mental State Examination (K-MMSE)[42] score of ≥24 (Set 1) was used to generate the HVa value. The right and left HV were averaged, and a linear regression of HV versus ICV was performed within this population to calculate the residual HV for individuals, referred to as HVa. This value represents the deviation in cubic millimeter from the expected HV based on the ICV.[22] Another independent dataset comprising 1123 participants (CU, MCI, and dementia) from the 3T-MRI registry in SMC (set 2) was used to develop the HVa cutoff. The k-means clustering method was applied in this subset to determine the HVa cutoff. This method adopts a centroid-model approach to group data by computing a putative representative point (centroid) per group and assigns actual data points to a group based on their distance from the nearest centroid and the distance between the centroids. The centroid is a means vector, and 10,000 iterations were included in this study to prevent poor random seeding of initial clusters. The Euclidean distance was set as the distance metric. The analysis was limited to 2 clusters. Each participant was assigned a probability of belonging to cluster A (low HV) or cluster B (high HV). The k-means analysis determined this value to be −0.478 cm^3 when the HVa cutoff value for defining neurodegeneration (N+/N–) was set to the 10th percentile of cluster B.[43]

Definition of Aβ Positivity Based on Amyloid PET

The Aβ PET images were co-registered on individual three-dimensional (3D)-T1 weighted MR images normalized to the T1-weighted MNI-152 template using Statistical Parametric Mapping (SPM) 8. The standardized uptake value ratio (SUVR) of the ^{18}F-florbetaben (FBB) or ^{18}F-flutemetamol (FMM) cortical target volume of interest was directly converted into a direct comparison of Centiloid units (dcCL) using the dcCL conversion equation from our previous study.[44,45] Cerebral cortex segmentation was performed using the segmentation method on the SPM8 and automatic anatomic labeling template. The whole-cerebellum mask was downloaded from the website of the Global Alzheimer's Association Interactive Network (http://www.gaain.org). No corrections were applied to the PET images for brain atrophy or partial-volume effects. The FBB-FMM cortical target region volume of interest-derived SUVR was converted to dcCL using a transformation equation derived from previous studies of FBB ($dcCL_{FBB} = 151.42 \times dcSUVR_{FBB} - 142.24$) and FMM ($dcCL_{FMM} = 148.52 \times dcSUVR_{FMM} - 137.09$).[45]

Receiver operating characteristic analysis was performed for each PET scan using Aβ positivity based on the SUVR cutoff as the standard to determine the dcCL cutoff value. Aβ positivity (A+) was defined according to the cutoff value of the FBB or FMM PET global dcCL, which was previously computed as 25.11.[46] Representative images showing negative and positive findings on Aβ PET scans are presented in Figures 1C–F.

Definition of A/N Classification

The HVa cutoff values were used to classify the participants into the following subgroups based on the Aβ and neurodegeneration status: Aβ negative and neurodegeneration negative (A–N–), Aβ negative and neurodegeneration positive (A–N+, SNAP), Aβ positive and neurodegeneration negative (A+N–), and Aβ positive and neurodegeneration positive (A+N+) subgroups.

Neuropsychological Tests and Longitudinal Assessment

All participants underwent neuropsychological tests using SNSB,[29,47] which assesses attention, language, visuospatial function, verbal and visual memory, and frontal/executive function. Composite scores for each cognitive domain were generated as follows: attention domain from Digit Span forward and backward scores (total: 17), language domain from the Korean version of the Boston Naming Test (total: 60), visuospatial function from the Rey Complex Figure Test (RCFT) copy score (total: 36), memory domain from the sum of delayed-recall scores of the Seoul Verbal Learning Test and RCFT (total: 48), and frontal/executive function from phonemic and semantic controlled oral word association tests and the Stroop color test (total: unlimited). The longitudinal SNSB results were obtained for 1310 participants over an average follow-up of 4.1 ± 3.1 years, with 2–16 time points.

Statistical Analysis

The demographics and clinical characteristics of the 3 A/N groups were compared using an analysis of variance model and χ^2 tests, as appropriate, to investigate the characteristics of the A–N+ subgroup compared with those of the control (A–N–) and AD with high likelihood (A+N+) subgroups.

A MATLAB toolbox was used for the cortical thickness analysis of the MRI data from participants. The localized differences in cortical thickness among the subgroups were analyzed using a general linear model to identify the cortical thinning pattern in subgroups after controlling for age, sex, education years, and ICV. The threshold for the statistical maps was set at $P < 0.05$ using the random field theory. Post hoc analysis was performed with Bonferroni adjustment.

Analysis of covariance was performed using age, sex, and education years as covariates to compare the cognitive profiles among the subgroups. Post hoc analysis was performed with a Bonferroni adjustment. A linear mixed effects model, with fixed effects of age, sex, education years, A/N subgroups, baseline score for each cognitive domain of neuropsychological tests, and time interval (between baseline and assessments), was used to investigate the differences

in cognitive trajectories across the three A/N subgroups. A two-way interaction term for time interval and A/N subgroups [age, sex, education, A/N subgroups, time interval (t), A/N subgroups × time interval (t)] was used. The patients were included as random effects. A log transformation was applied to the memory domain score variable, which had high skewness.

All statistical analyses were performed with R (version 1.2.5). Statistical significance was set at two-tailed $P < 0.05$.

RESULTS

Clinical Characteristics According to the A/N Biomarker Subgroups

The CSVD(–) cohort comprised 513 CU participants, 469 participants with MCI, and 380 participants with dementia. The average age of the participants in the CSVD(–) cohort was 71.1 ± 8.1 years, with women accounting for 56.4% of the cohort population and *APOE* ε4 carriers accounting for 38.9% of the cohort population. The CSVD(+) cohort comprised 53 CU participants, 172 participants with MCI, and 173 participants with dementia. The average age of the participants in the CSVD(+) was 76.2 ± 6.7 years, with women accounting for 66.3% of the cohort population and ε4 carriers accounting for 25.2% of the cohort population. Figure 2 presents the distribution of each A/N group according to cognitive status and CSVD burden. Particularly, SNAP (A–N+) was more prevalent among the A– participants in the CSVD(+) cohort than those in the CSVD(–) cohort (58.4% vs. 25.8%). Table 1 presents the detailed demographics and characteristics of participants.

Within the CSVD(–) cohort, at the CU and MCI stages, A–N+ participants were older than those in A–N–. At the MCI and dementia stages, A–N+ was significantly older than A+N+. No differences were observed between the A–N+ and other subgroups in terms of education years according to cognitive status. No differences were observed between A–N– and A–N+ in the prevalence of ε4 carriers across all cognitive statuses; however, the proportion of ε4 carriers in A+N+ was significantly higher than in A–N– and A–N+. Among the CU participants, the prevalence of hypertension (HTN) and diabetes mellitus (DM) in A–N+ was higher than in A–N–. Among the participants with MCI, the prevalence of DM in A–N+ was significantly higher than in A+N+. Among the participants with dementia, the prevalence of HTN and DM in A–N+ was higher than in A+N+; the prevalence of DM in A–N+ was also higher than in A–N–. No significant differences were observed between A–N+ and A–N–in terms of the Aβ PET uptake across all cognitive statuses.

Among participants in the CSVD(+) cohort, A–N+ was significantly older than A–N–across all cognitive statuses. Participants with dementia in A–N+ were younger than those in A+N+. No differences were observed in sex and educational years according to cognitive status. Similar to the CSVD(–) cohort, no difference was observed between A–N– and A–N+ in the proportion of ε4 carriers; however, the proportion of ε4 carriers in A+N+ was higher than in A–N– and A–N+. Notably, the distribution of vascular risk factors such as HTN and DM did not differ across cognitive statuses. No significant differences in Aβ PET uptake were observed between A–N+ and A–N–across all cognitive statuses.

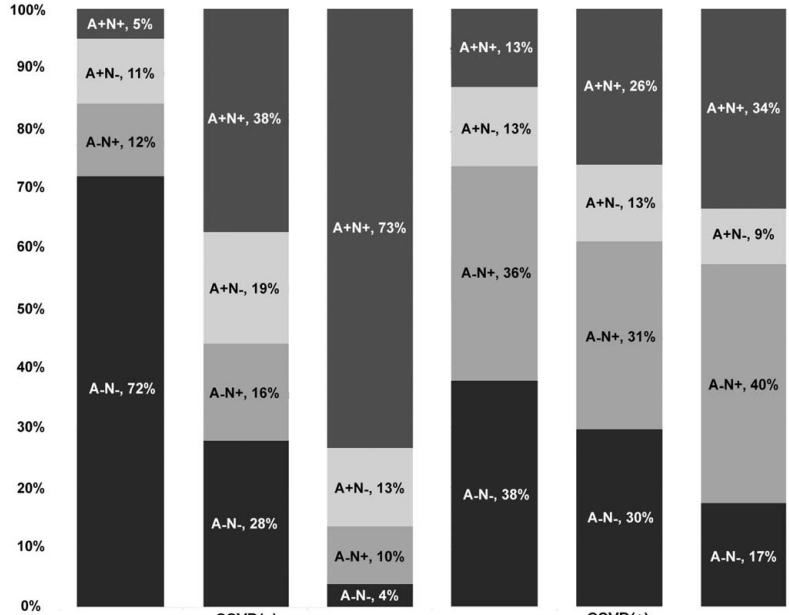

FIGURE 2. Distribution of the A/N biomarker subgroups based on the cognitive status and CSVD burden. A indicates β-amyloid; CSVD, cerebral small vessel disease; CU, cognitively unimpaired; N, neurodegeneration; MCI, mild cognitive impairment.

TABLE 1. Demographics and Clinical Characteristics of the A/N Biomarker Subgroups

CSVD(–)

	CU				MCI				Dementia			
	A–N–	**A–N+**	**A+N+**		**A–N–**	**A–N+**	**A+N+**		**A–N–**	**A–N+**	**A+N+**	
N	**413**	**70**	**30**	***P***	**160**	**93**	**216**	***P***	**17**	**42**	**321**	***P***
Age, y	69.2 ± 7.1	75.7 ± 7.0*	76.8 ± 5.3*	< 0.001	67.6 ± 7.4	75.8 ± 6.5*	73.0 ± 7.9*†	< 0.001	73.7 ± 7.1	77.1 ± 8.2	70.8 ± 8.8†	< 0.001
Women, N (%)	257 (62.2)	34 (48.6)	21 (70.0)	0.055	73 (45.6)	42 (45.2)	113 (52.3)	0.333	3 (17.6)	23 (54.8)	188 (58.6)*	0.004
Education, y	11.9 ± 4.7	12.4 ± 4.8	10.4 ± 4.7	0.169	12.4 ± 4.5	11.7 ± 5.0	11.8 ± 4.9	0.427	10.2 ± 5.6	9.9 ± 6.2	11.4 ± 4.8	0.154
APOE ε4 carrier, N (%)	71 (17.5)	11 (16.4)	14 (48.3)*†	< 0.001	25 (16.2)	17 (18.9)	142 (66.0)*†	< 0.001	3 (20.0)	3 (7.5)	198 (62.9)*†	< 0.001
Vascular risk factor, N (%)												
Hypertension	153 (42.4)	43 (68.3)*	13 (46.4)	0.001	67 (43.5)	43 (46.2)	81 (37.9)	0.318	10 (58.8)	25 (59.5)	129 (40.4)†	0.027
Diabetes mellitus	64 (17.7)	24 (38.1)*	8 (28.6)	0.001	28 (18.2)	28 (30.1)	31 (14.5)†	0.006	8 (47.1)	23 (54.8)*	50 (15.7)†	< 0.001
K-MMSE	28.2 ± 1.9	27.5 ± 2.7*	27.2 ± 2.0*	0.001	27.0 ± 2.6	25.1 ± 3.5*	24.4 ± 3.6*	< 0.001	22.7 ± 4.7	19.9 ± 4.8	18.8 ± 5.6*	0.013
Aβ PET Centiloid unit	3.31 ± 7.89	1.71 ± 9.01	72.55 ± 32.11*†	< 0.001	3.72 ± 7.55	0.94 ± 10.62	91.44 ± 31.20*†	< 0.001	−1.09 ± 7.53	−1.14 ± 11.58	102.06 ± 30.88*†	< 0.001
CSVD(+)												
	CU				MCI				Dementia			
	A–N–	A–N+	A+N+		A–N–	A–N+	A+N+		A–N–	A–N+	A+N+	
N	20	19	7	*P*	51	54	45	*P*	30	69	58	*P*
Age, y	70.8 ± 6.2	78.0 ± 6.8*	83.6 ± 2.5*	< 0.001	71.5 ± 5.8	77.8 ± 5.6*	79.1 ± 5.0*	< 0.001	70.5 ± 7.6	77.3 ± 5.9*	79.9 ± 4.8*†	< 0.001
Women, N (%)	13 (65.0)	15 (78.9)	6 (85.7)	0.454	28 (54.9)	35 (64.8)	30 (66.7)	0.430	18 (60.0)	51 (73.9)	39 (67.2)	0.370
Education, years	11.0 ± 5.6	7.7 ± 4.3	11.3 ± 4.3	0.081	10.0 ± 5.7	10.5 ± 5.1	10.0 ± 5.8	0.879	8.4 ± 4.6	9.2 ± 5.4	9.6 ± 5.7	0.596
APOE ε4 carrier, N (%)	2 (10.0)	1 (5.3)	3 (42.9)	0.036	8 (15.7)	8 (14.8)	19 (42.2)*†	0.002	3 (10.0)	11 (15.9)	26 (45.6)*†	< 0.001
Vascular risk factor, N (%)												
Hypertension	13 (65.0)	11 (57.9)	5 (71.4)	0.794	44 (86.3)	39 (72.2)	29 (64.4)	0.043	24 (80.0)	55 (79.7)	41 (70.7)	0.431
Diabetes mellitus	2 (10.0)	3 (15.8)	2 (28.6)	0.498	18 (35.3)	22 (40.7)	13 (28.9)	0.470	10 (33.3)	29 (42.0)	15 (25.9)	0.160
K-MMSE	27.3 ± 2.0	26.3 ± 2.9	25.3 ± 2.8	0.175	26.1 ± 3.3	24.9 ± 3.6	24.2 ± 4.2	0.054	21.1 ± 3.9	19.2 ± 4.5	19.1 ± 5.2	0.113
Aβ PET Centiloid unit	1.48 ± 7.71	2.60 ± 11.71	71.43 ± 38.17*†	< 0.001	2.11 ± 9.05	3.14 ± 10.89	78.29 ± 33.79*†	< 0.001	3.65 ± 9.12	−2.06 ± 10.98	88.57 ± 34.09*†	< 0.001

Data are expressed as number (proportion) or mean ± SD.

*$P < 0.05$ compared with the A–N– subgroup.

†$P < 0.05$ compared with the A–N+ subgroup.

A indicates β-amyloid; *APOE*, apolipoprotein; Aβ, β-amyloid; CSVD, cerebral small vessel disease; CU, cognitively unimpaired; K-MMSE, Korean-Mini Mental State Examination; MCI, mild cognitive impairment; N, neurodegeneration.

TABLE 2. Cortical Thickness of the MRI Structural Measures According to A/N Biomarker Subgroups and CSVD Burden

CSVD(–)												
	CU				**MCI**				**Dementia**			
	A–N–	**A–N+**	**A+N+**		**A–N–**	**A–N+**	**A+N+**		**A–N–**	**A–N+**	**A+N+**	
N (%)	**413**	**70**	**30**	***P***	**160**	**93**	**216**	***P***	**17**	**42**	**321**	***P***
Cingulate	3.25 ± 0.14	3.22 ± 0.14	3.14 ± 0.16*†	< 0.001	3.26 ± 0.17	3.16 ± 0.15*	3.16 ± 0.15*	< 0.001	3.13 ± 0.20	3.10 ± 0.16	3.04 ± 0.20	0.039
Frontal	3.16 ± 0.09	3.09 ± 0.10*	3.07 ± 0.12*	< 0.001	3.17 ± 0.10	3.07 ± 0.11*	3.08 ± 0.12*	< 0.001	3.08 ± 0.14	2.95 ± 0.17*	3.01 ± 0.15	0.009
Parietal	3.09 ± 0.10	3.02 ± 0.11*	2.98 ± 0.14*	< 0.001	3.11 ± 0.12	2.99 ± 0.11*	2.98 ± 0.14*	< 0.001	3.01 ± 0.20	2.90 ± 0.16	2.88 ± 0.20*	0.016
Temporal	3.30 ± 0.10	3.24 ± 0.13*	3.18 ± 0.13*	< 0.001	3.31 ± 0.12	3.17 ± 0.12*	3.18 ± 0.15*	< 0.001	3.21 ± 0.16	3.07 ± 0.17*	3.06 ± 0.19*	0.004
Occipital	3.00 ± 0.15	2.92 ± 0.17*	2.87 ± 0.17*	< 0.001	3.02 ± 0.15	2.85 ± 0.15*	2.87 ± 0.15*	< 0.001	2.88 ± 0.18	2.79 ± 0.12	2.79 ± 0.18	0.122
CSVD(+)												
	CU				MCI				Dementia			
	A–N–	A–N+	A+N+		A–N–	A–N+	A+N+		A–N–	A–N+	A+N+	
N (%)	20	19	7	*P*	51	54	45	*P*	30	69	58	*P*
Cingulate	3.23 ± 0.16	3.15 ± 0.12	3.26 ± 0.14	0.094	3.21 ± 0.12	3.13 ± 0.16*	3.18 ± 0.18	0.017	3.14 ± 0.11	3.08 ± 0.15	3.11 ± 0.15	0.136
Frontal	3.14 ± 0.09	3.07 ± 0.11	3.07 ± 0.07	0.071	3.14 ± 0.08	3.07 ± 0.11*	3.09 ± 0.12*	0.001	3.11 ± 0.10	3.03 ± 0.14*	3.04 ± 0.14	0.044
Parietal	3.10 ± 0.11	3.07 ± 0.12	2.97 ± 0.08*	0.036	3.09 ± 0.10	3.01 ± 0.12*	3.02 ± 0.13*	0.001	3.03 ± 0.10	3.01 ± 0.15	2.99 ± 0.15	0.433
Temporal	3.27 ± 0.10	3.21 ± 0.09	3.15 ± 0.06*	0.014	3.27 ± 0.10	3.16 ± 0.12*	3.17 ± 0.13*	< 0.001	3.22 ± 0.08	3.13 ± 0.14*	3.11 ± 0.14*	0.002
Occipital	2.97 ± 0.13	2.96 ± 0.15	2.83 ± 0.08	0.064	2.96 ± 0.11	2.85 ± 0.13*	2.87 ± 0.15*	< 0.001	2.93 ± 0.09	2.86 ± 0.14	2.85 ± 0.16*	0.039

Data are expressed as mean ± SD. The *P*-values were obtained by analysis of covariance model adjusted for age, sex, and education.
*$P < 0.05$ compared with the A–N– group.
†$P < 0.05$ compared with the A–N+ group.
A indicates β-amyloid; CSVD, cerebral small vessel disease; CU, cognitively unimpaired; MCI, mild cognitive impairment; N, neurodegeneration.

Comparison of Cortical Thickness According to A/N Biomarker Subgroups

Table 2 presents the differences in cortical thickness among A–N–, A–N+, and A+N+ according to cognitive status. In the CSVD(–) cohort, at the CU stage, cortical thickness in A–N+ and A+N+ was lower than in A–N–in the frontal, parietal, temporal, and occipital regions. A significant difference in cortical thickness was observed between A–N+ and A+N+ only in the cingulate region. At the MCI stage, the cortical thickness in A–N+ and A+N+ was lower than in A–N–in widespread cortical regions. However, at the dementia stage, cortical thickness in A–N+ was lower than in A–N–only in the frontal and temporal regions. No significant differences were observed between A–N+ and A+N+ in cortical thickness in the MCI and dementia stages.

In the CSVD(+) cohort, CU participants showed no significant differences between A–N+ and A–N– in cortical thickness. However, participants with MCI in A–N+ exhibited more pronounced atrophy than in A–N– across widespread cortical regions. Similarly, participants with dementia in A–N+ exhibited greater atrophy in the frontal and temporal regions than in A–N–. No significant differences were observed between A–N+ and A+N+ in cortical thickness across all cognitive statuses.

Comparison of Cross-sectional and Longitudinal Cognition According to the A/N Biomarker Subgroups

Table 3 presents the comparison of cognition among the A/N biomarker subgroups according to cognitive status and CSVD burden. Among the CSVD(–) cohort, at the CU stage, A–N+ had significantly lower scores in the memory, language, and frontal/executive domains, and the K-MMSE scores compared with A–N–. No significant differences were observed between the CU participants in A–N+ and A+N+ across all cognitive domains. However, at the MCI stage, A–N+ exhibited higher scores in the memory domain and lower scores in the language domain compared with A+N+. No significant differences were observed at the dementia stage between A–N+ and A+N+ in terms of the cognitive domain and K-MMSE scores; however, A–N+ exhibited better performance in the memory domain compared with A+N+.

Among the CSVD(+) cohort, CU participants in A–N + had lower scores in the memory domain than those in A–N– ($P < 0.05$); however, no significant differences were noted in other cognitive domains. At the MCI stage, A–N+ had lower language scores than A–N–, while their memory scores were higher than those in A+N+. In participants with dementia, memory scores in A–N+ were lower than in A–N–; however, no significant differences were observed across cognitive domains in A+N+.

Supplementary Table 2, Supplemental Digital Content 1, http://links.lww.com/CNM/A539 presents the results of the comparison of longitudinal cognition according to the 3 A/N subgroups for each cognitive status. Figure 3 depicts representative domains. Among the participants in the CSVD(–) cohort, CU participants in A–N+ exhibited worse trajectories in the memory, language, visuospatial, and frontal/executive domains compared with A–N–. Compared with A+N+, A–N+ demonstrated better trajectories in the memory domain and K-MMSE. Similarly, among participants with MCI, A–N+ exhibited worse trajectories across all cognitive domains and K-MMSE compared with A–N–, while exhibiting better trajectories in memory, language, and frontal/executive domains and K-MMSE than A+N+. For participants with dementia, no differences were observed between A–N+ and A–N–across all cognitive domains; however, A–N+ exhibited a better trajectory in the frontal/executive domain than in A+N+.

Within the CSVD(+) cohort, CU participants showed no significant difference across the 3 A/N subgroups for all cognitive domains. For participants with MCI, A–N+ exhibited steeper slopes in the memory and language domains and K-MMSE than A–N–, while no differences were found between A–N+ and A+N+ across all cognitive domains. Among participants with dementia, no differences were observed between A–N+ and A–N– in any cognitive domains. However, A–N+ exhibited better trajectory in the language and frontal/executive domains, as well as K-MMSE scores, compared with A+N+.

DISCUSSION

The present study investigated the clinical and imaging characteristics of A/N subgroups, particularly focusing on SNAP, in a memory clinic cohort encompassing varying cognitive status and CSVD burden. The main findings are as follows (Table 4). First, in the CSVD(–) cohort, participants with SNAP (A–N+) were older and had more vascular risk factors than those in A–N– or A+N+; however, these characteristics were not observed in the SNAP group within the CSVD(+) cohort. Second, SNAP and A+N+ exhibited similar cortical thinning regardless of the cognitive status and CSVD burden. Lastly, SNAP exhibited cognitive decline, although the progression varied compared with A–N– or A+N+ according to cognitive status and CSVD burden. Taken together, these findings suggest that compared with their biomarker counterparts such as A–N– or A +N+, SNAP has distinct characteristics (encompassing demographics, cortical thickness, and cognitive decline) that vary according to the cognitive status and CSVD burden.

The proportion of SNAP among the A– participants was higher in the presence of CSVD burden than that observed in its absence, indicating that SNAP is associated with CSVD burden. Hippocampal atrophy without Aβ deposition can develop from non-Aβ pathways such as CSVD, Lewy body disease, TAR DNA-binding protein 43 (TDP-43) proteinopathy, limbic-predominant age-related TDP-43 encephalopathy (LATE), primary age-related tauopathy (PART), hippocampal sclerosis, or argyrophilic grain disease.[12,21,48–50] The present study revealed that CSVD is closely associated with neurodegeneration and cognitive impairment in the absence of Aβ, which may be mediated by various mechanisms.[12,51–54] This assumption is supported by earlier findings demonstrating that SNAP had more vascular burden than that in the A–N– or A+ populations.[12,14,48,50]

The first major finding of the present study was that SNAP exhibited distinct clinical characteristics compared with its biomarker counterparts (A–N– or A+N+) depending on cognitive status and CSVD burden. In the CU and MCI stages, individuals with SNAP were older than those in A–N–, regardless of the CSVD burden, consistent with previous studies suggesting that age-related pathology contributes to neurodegeneration.[12] However, in the MCI and dementia stages of the CSVD(–) cohort, those with

TABLE 3. Comparison of Cognition According to the A/N Biomarker Subgroups and CSVD Burden

	CU				MCI				Dementia			
CSVD(–)	**A–N–**	**A–N+**	**A+N+**		**A–N–**	**A–N+**	**A+N+**		**A–N–**	**A–N+**	**A+N+**	
N	**413**	**70**	**30**	***P***	**160**	**93**	**216**	***P***	**17**	**42**	**321**	***P***
Memory	23.1 ± 7.3	19.0 ± 7.9*	15.4 ± 5.0*	< 0.001	14.1 ± 7.5	8.5 ± 5.4*	4.8 ± 4.7*†	< 0.001	3.9 ± 4.5	3.3 ± 4.2	1.7 ± 3.1*†	0.001
Attention	10.5 ± 2.5	10.1 ± 2.4	9.1 ± 2.1*	0.015	9.8 ± 2.2	9.1 ± 2.3	9.4 ± 2.4	0.083	7.8 ± 2.7	7.2 ± 2.4	8.1 ± 2.5	0.131
Language	49.5 ± 6.2	46.8 ± 8.3*	44.2 ± 8.0*	< 0.001	43.8 ± 9.1	36.9 ± 11.7*	40.1 ± 10.5*†	< 0.001	38.4 ± 9.1	30.4 ± 10.7	32.2 ± 14.0	0.138
Visuospatial	32.8 ± 3.6	32.2 ± 4.7	32.6 ± 2.9	0.398	30.1 ± 6.5	28.5 ± 7.8	28.5 ± 7.4	0.102	23.8 ± 8.8	22.1 ± 11.0	20.6 ± 12.1	0.457
Frontal/executive	130.2 ± 32.3	116.2 ± 36.7*	108.2 ± 26.5*	< 0.001	112.6 ± 34.6	79.2 ± 38.1*	90.8 ± 41.3*	< 0.001	66.3 ± 43.1	51.0 ± 34.7	51.8 ± 38.4	0.327
K-MMSE	28.2 ± 1.9	27.5 ± 2.7*	27.2 ± 2.0*	0.001	27.0 ± 2.6	25.1 ± 3.5*	24.4 ± 3.6*	< 0.001	22.7 ± 4.7	19.9 ± 4.8	18.8 ± 5.6*	0.013
CSVD(+)		CU				MCI				Dementia		
	A–N–	A–N+	A+N+		A–N–	A–N+	A+N+		A–N–	A–N+	A+N+	
N	20	19	7	*P*	51	54	45	*P*	30	69	58	*P*
Memory	22.6 ± 6.3	15.0 ± 7.1*	15.4 ± 6.0*	0.002	13.3 ± 7.0	10.5 ± 6.5	6.6 ± 5.8*†	< 0.001	6.6 ± 6.1	3.8 ± 4.3*	2.5 ± 3.3*	< 0.001
Attention	9.2 ± 1.9	8.9 ± 1.9	9.1 ± 1.5	0.935	8.5 ± 2.1	8.4 ± 1.9	8.6 ± 1.9	0.960	7.1 ± 2.1	7.3 ± 2.5	7.5 ± 1.7	0.703
Language	45.6 ± 7.1	43.1 ± 10.9	40.0 ± 10.3	0.374	42.0 ± 8.4	36.4 ± 10.7*	36.8 ± 9.5*	0.006	33.0 ± 8.6	30.2 ± 10.0	27.9 ± 11.1	0.089
Visuospatial	32.4 ± 3.1	29.5 ± 4.3	29.2 ± 4.9	0.056	28.3 ± 7.7	26.2 ± 8.8	26.6 ± 7.7	0.365	21.2 ± 9.1	18.4 ± 10.3	21.9 ± 9.8	0.137
Frontal/executive	109.2 ± 30.1	96.4 ± 39.3	92.0 ± 22.3	0.365	88.0 ± 31.3	74.6 ± 36.3	76.9 ± 31.5	0.097	41.3 ± 29.4	40.6 ± 29.9	45.8 ± 27.6	0.600
K-MMSE	27.3 ± 2.0	26.3 ± 2.9	25.3 ± 2.8	0.175	26.1 ± 3.3	24.9 ± 3.6	24.2 ± 4.2	0.054	21.1 ± 4.0	19.2 ± 4.5	19.1 ± 5.2	0.113

Data are expressed as mean ± standard deviation. The *P*-values were obtained by analysis of covariance model adjusted for age, sex, and education.
*$P < 0.05$ compared with the A–N– group.
†$P < 0.05$ compared with the A–N+ group.
A indicates β-amyloid; CSVD, cerebral small vessel disease; CU, cognitively unimpaired; K-MMSE, Korean-Mini Mental State Examination; MCI, mild cognitive impairment; N, neurodegeneration.

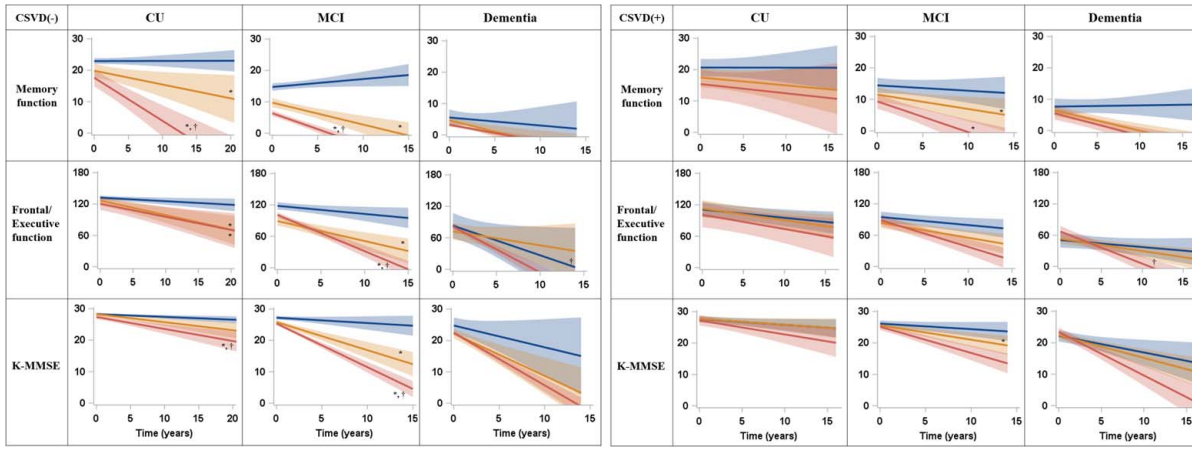

FIGURE 3. Distinctive cognitive trajectories according to the A/N biomarker and CSVD burden. The *y*-axis represents the predicted cognitive function scores for each follow-up year derived from the predicted model equation using a linear mixed effect model. The blue line is the A–N– subgroup; the orange line is the A–N+ subgroup; and the red line is A+N+ subgroup. *$P < 0.05$ compared with A–N– group; †$P < 0.05$ compared with A–N+ group. CU indicates cognitively unimpaired; MCI, mild cognitive impairment.

SNAP were older than A+N+. In contrast, in the CSVD(+) cohort, participants in A+N+ were older than those with SNAP. These findings suggest that the pathology underlying SNAP, which contributes to cognitive impairment in the absence of CSVD (severe WMH), is associated with age. Conversely, in the presence of CSVD, older age is predictive of Aβ positivity.[55] The prevalence of *APOE* ε4 carriers in A–N+ was lower than in A+N+ for all cognitive statuses, regardless of CSVD. The *APOE* ε4 allele is a major risk factor for Aβ deposition;[56,57] thus, the prevalence of ε4 carriers among SNAP participants is expected to be lower than in A+N+, consistent with previous studies.[8,12] Compared with A–N–, the SNAP (A–N+) showed no differences in ε4 carrier prevalence or quantitative Aβ uptake, arguing against the possibility of subclinical (subthreshold) Aβ deposition in SNAP. Thus, neurodegeneration in SNAP might progress via a pathway unrelated to the *APOE* ε4 allele and Aβ deposition. In the CSVD(–) cohort, SNAP had a higher ratio of vascular risk factors, such as HTN or DM, compared with A–N– or A+N+ in the present study. This finding aligns with earlier studies demonstrating that SNAP-CU had a higher ratio of vascular risk factors than A–N– CU individuals,[12] and that HTN was more frequently observed in A– than A+ individuals with dementia.[20] Therefore, vascular risk factors may be one of the main contributors to neurodegeneration, leading to cognitive impairment in the absence of a marker of severe CSVD on MRI.

The second major finding of the present study was that SNAP and A+N+ exhibited similar cortical thinning in widespread regions, regardless of the cognitive status and CSVD burden, despite neurodegeneration being defined based on HV atrophy only. In the CSVD(–) CU group; however, SNAP showed a preserved cingulate cortex compared with A+N+. These findings align with previous studies, indicating that SNAP exhibits a structural neurodegeneration pattern similar to preclinical AD (A+ CU)[54] and prodromal AD (A+ MCI).[15] Notably, in the MCI and dementia stages across both CSVD(–) and CSVD(+) cohorts, SNAP exhibited more pronounced cortical thinning than A–N–, but no significant differences compared with A+N+. The similarity in cortical thinning between SNAP and

TABLE 4. Summary of Clinical Outcomes Across Cohorts

Cohort		Key findings	
CSVD(–)	General	SNAP is older and more likely to have vascular risk factors than A–N– and A+N+.	
	Cognitive Status	Cortical thinning	Cognition
	CU	SNAP exhibits cortical thinning similar to A+N+ but preserved cingulate cortex.	SNAP shows worse cognitive decline than A–N– but less decline in memory than A+N+
	MCI	SNAP exhibits cortical thinning similar to A+N+	SNAP shows worse cognitive decline than A–N– but less decline than A+N+
	Dementia	SNAP exhibits cortical thinning similar to A+N+	No differences were observed in cognitive trajectories between SNAP and A+N+, except in the frontal/executive domain, where A+N+ showed more rapid decline.
CSVD(+)	General	SNAP is younger than A+N+	
	Cognitive Status	Cortical thinning	Cognition
	CU/MCI	SNAP and A+N+ exhibited similar cortical thinning	SNAP showed a similar cognitive trajectory with A+N+
	Dementia	SNAP and A+N+ exhibited similar cortical thinning	SNAP exhibited better trajectory in the language and frontal/executive domains, as well as K-MMSE scores, compared with A+N+.

A+N+ suggests that non-Aβ pathways, including old age, vascular risk factors, TDP-43 proteinopathy, LATE, or PART, may drive comparable neurodegeneration. TDP-43 and tau pathology are known to contribute to hippocampal and entorhinal cortex atrophy in the absence of Aβ.[58] Tau pathology in PART, which extends beyond the medial temporal lobe, may directly involve the medial parietal and lateral temporal/parietal cortex, functionally connected to the medial temporal lobe through the posterior default mode network.[59,60] Given that similar cortical thinning may result from distinct underlying pathologic mechanisms, it is crucial to account for diverse contributors when evaluating neurodegeneration.

The final major finding of the present study was that participants with SNAP exhibited cognitive decline, with variations in progression compared with A–N– or A+N+, based on the cognitive status and CSVD burden. Specifically, in the CSVD(–) cohort, SNAP-CU, and SNAP-MCI had lower cognitive function scores and worse trajectories in memory, language, and frontal/executive domains than A–N– CU and A–N– MCI, respectively. Conversely, no differences were observed between SNAP-CU and A+N+ CU in cognitive function, except for a longitudinal divergence in the memory domain favoring SNAP-CU. SNAP-MCI demonstrated better baseline memory function and preserved cognitive trajectories in memory, language, and frontal/executive domains compared with A+N+ MCI. At the dementia stage, no differences were observed in the cognitive trajectories between SNAP-dementia and A+N+ dementia, except in the frontal/executive domain, where A+N+ dementia showed more rapid decline. Thus, in the CSVD(–) cohort, SNAP exhibited overall worse cognitive decline than A–N– but a better trajectory than A+N+ in both CU and MCI stages. In the dementia stage, SNAP dementia exhibited cognitive decline similar to A–N– and A+N+.

In the CSVD(+) cohort, no significant differences in cognitive trajectories were observed at the CU stage, except in the language domain, where A+N+ exhibited the fastest decline. At the MCI stage, SNAP-MCI experienced greater cognitive decline in memory and language domains than A–N–. In the dementia stage, SNAP exhibited less deterioration in language and frontal/executive domains than A+N+. Overall, in the CSVD(+) cohort, SNAP showed a similar cognitive decline compared with A+N+ in the CU and MCI stages; however, SNAP-dementia exhibited less cognitive decline than those in A+N+. Although several previous studies have suggested that SNAP might be benign,[4,61] the present study demonstrated that SNAP without CSVD burden aligns with AD-like cortical thinning and cognitive trajectory. Conversely, in SNAP-dementia with CSVD burden, vascular pathology likely contributed primarily to cognitive impairment, independent of Aβ-related pathology. In contrast, A+N+ dementia with CSVD burden had additional AD pathology, which could explain why SNAP dementia showed a better cognitive trajectory than A+N+ dementia. Our findings align with earlier studies indicating that CSVD and Aβ-related pathology may synergistically contribute to cognitive decline,[62–65] through disrupted microvascular integrity, neuroinflammation, and blood-brain barrier dysfunction.[66,67] These interactions underscore the importance of targeting both vascular and Aβ-related mechanisms to mitigate cognitive decline effectively.

The strength of the present study is the detailed investigation of clinical and imaging characteristics of SNAP according to cognitive status and CSVD burden, which helps to clarify SNAP's distinctive features. However, there are some limitations. First, due to the lack of autopsy data, the clustering methods for SNAP detection and underlying pathologies could not be fully validated. Second, neurodegeneration was defined solely by HVa, given hippocampal atrophy's clinical relevance,[68] though it may not capture all neurodegeneration types. Further studies using other neurodegeneration biomarkers could be helpful to support these findings. Third, CSVD burden was defined using severe WMH based on the classification system for ischemia,[30] rather than lacunes or microbleeds. However, our previous validation study suggested the severe WMH classification system could distinguish the severity of CSVD,[30] and would be appropriate as a representative system for CSVD burden.

Nevertheless, the present study is valuable as its findings indicate that SNAP does not exhibit a benign course and may present a pattern of cortical thinning and cognitive decline similar to that of AD, particularly in the absence of CSVD. Although previous studies have investigated the characteristics of SNAP, especially in CU or MCI statuses, the present study characterized SNAP in a large memory clinic cohort that included patients with dementia and CSVD burden. SNAP is associated with distinctive clinical and imaging characteristics such as a higher number of vascular risk factors and older age, which might be related to neurodegeneration. The clinical implications of SNAP, particularly concerning cognitive trajectory, should be interpreted differently according to the cognitive status and CSVD burden.

REFERENCES

1. Schneider JA, Arvanitakis Z, Bang W, et al. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology*. 2007;69:2197–2204.
2. Matej R, Tesar A, Rusina R. Alzheimer's disease and other neurodegenerative dementias in comorbidity: a clinical and neuropathological overview. *Clin Biochem*. 2019;73:26–31.
3. Kapasi A, DeCarli C, Schneider JA. Impact of multiple pathologies on the threshold for clinically overt dementia. *Acta Neuropathol*. 2017;134:171–186.
4. Mormino EC, Betensky RA, Hedden T, et al. Synergistic effect of β-amyloid and neurodegeneration on cognitive decline in clinically normal individuals. *JAMA Neurol*. 2014;71:1379–1385.
5. Mormino E, Kluth J, Madison C, et al. Episodic memory loss is related to hippocampal-mediated β-amyloid deposition in elderly subjects. *Brain*. 2009;132:1310–1323.
6. Brayne C, Richardson K, Matthews FE, et al. Neuropathological correlates of dementia in over-80-year-old brain donors from the population-based Cambridge city over-75s cohort (CC75C) study. *J Alzheimers Dis*. 2009;18:645–658.
7. Risacher SL, Saykin AJ. Neuroimaging biomarkers of neurodegenerative diseases and dementia. *Seminars in neurology*, Thieme Medical Publishers, 2013;33:386-416.
8. Jack CR Jr, Knopman DS, Weigand SD, et al. An operational approach to National Institute on Aging-Alzheimer's Association criteria for preclinical Alzheimer disease. *Ann Neurol*. 2012;71:765–775.
9. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7:280–292.
10. 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;7:270–279.
11. 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;7:263–269.
12. Knopman DS, Jack CR Jr, Wiste HJ, et al. Brain injury biomarkers are not dependent on β-amyloid in normal elderly. *Ann Neurol*. 2013;73:472–480.
13. Vos SJ, Xiong C, Visser PJ, et al. Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study. *Lancet Neurol*. 2013;12:957–965.
14. Knopman DS, Jack CR Jr, Wiste HJ, et al. Short-term clinical outcomes for stages of NIA-AA preclinical Alzheimer disease. *Neurology*. 2012;78:1576–1582.
15. Caroli A, Prestia A, Galluzzi S, et al. Mild cognitive impairment with suspected nonamyloid pathology (SNAP): prediction of progression. *Neurology*. 2015;84:508–515.
16. Petersen RC, Aisen P, Boeve BF, et al. Mild cognitive impairment due to Alzheimer disease in the community. *Ann Neurol*. 2013;74:199–208.
17. Prestia A, Caroli A, van der Flier WM, et al. Prediction of dementia in MCI patients based on core diagnostic markers for Alzheimer disease. *Neurology*. 2013;80:1048–1056.
18. Duara R, Loewenstein DA, Shen Q, et al. Amyloid positron emission tomography with 18F-flutemetamol and structural magnetic resonance imaging in the classification of mild cognitive impairment and Alzheimer's disease. *Alzheimers Dement*. 2013;9:295–301.
19. Wisse LEM, Butala N, Das SR, et al. Suspected non-AD pathology in mild cognitive impairment. *Neurobiol Aging*. 2015; 36:3152–3162.
20. Landau SM, Horng A, Fero A, et al. Amyloid negativity in patients with clinically diagnosed Alzheimer disease and MCI. *Neurology*. 2016;86:1377–1385.
21. Jack CR, Knopman DS, Chételat G, et al. Suspected non-Alzheimer disease pathophysiology—concept and controversy. *Nat Rev Neurology* . 2016;12:117–124.
22. Jack CR Jr, Wiste HJ, Weigand SD, et al. Different definitions of neurodegeneration produce similar amyloid/neurodegeneration biomarker group findings. *Brain*. 2015;138:3747–3759.
23. Jack CR Jr, Wiste HJ, Knopman DS, et al. Rates of beta-amyloid accumulation are independent of hippocampal neurodegeneration. *Neurology*. 2014;82:1605–1612.
24. Jack CR Jr, Wiste HJ, Weigand SD, et al. Age-specific population frequencies of cerebral beta-amyloidosis and neurodegeneration among people with normal cognitive function aged 50-89 years: a cross-sectional study. *Lancet Neurol*. 2014; 13:997–1005.
25. Kang Y, Jahng S, Na DL. *Seoul Neuropsychological Screening Battery*, 2nd Edition. Human Brain Research & Consulting Co; 2012.
26. Ryu HJ, Yang DW. The Seoul Neuropsychological Screening Battery (SNSB) for comprehensive neuropsychological assessment. *Dement Neurocogn Disord*. 2023;22:1.
27. Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14:535–562.
28. Christensen KJ, Multhaup KS, Nordstrom S, et al. A cognitive battery for dementia: Development and measurement characteristics. *Alzheimers Dement*. 1991;3:168.
29. Ahn HJ, Chin J, Park A, et al. Seoul Neuropsychological Screening Battery-dementia version (SNSB-D): a useful tool for assessing and monitoring cognitive impairments in dementia patients. *J Korean Med Sci*. 2010;25:1071–1076.
30. Noh Y, Lee Y, Seo SW, et al. A new classification system for ischemia using a combination of deep and periventricular white matter hyperintensities. *J Stroke Cerebrovasc Dis*. 2014;23: 636–642.
31. Kim S, Choi SH, Lee YM, et al. Periventricular white matter hyperintensities and the risk of dementia: a CREDOS study. *Int Psychogeriatr*. 2015;27:2069–2077.
32. Kang SH, Kim ME, Jang H, et al. Amyloid positivity in the Alzheimer/subcortical-vascular spectrum. *Neurology*. 2021;96: e2201–e2211.
33. Zijdenbos AP, Forghani R, Evans AC. Automatic "pipeline" analysis of 3-D MRI data for clinical trials: application to multiple sclerosis. *IEEE Trans Med Imaging*. 2002;21: 1280–1291.
34. Collins DL, Neelin P, Peters TM, et al. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. *J Comput Assist Tomogr*. 1994;18:192–205.
35. Sled JG, Zijdenbos AP, Evans AC. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Trans Med Imaging*. 1998;17:87–97.
36. Lerch JP, Evans AC. Cortical thickness analysis examined through power analysis and a population simulation. *Neuroimage*. 2005;24:163–173.
37. Im K, Lee JM, Lee J, et al. Gender difference analysis of cortical thickness in healthy young adults with surface-based methods. *Neuroimage*. 2006;31:31–38.
38. Lyttelton O, Boucher M, Robbins S, et al. An unbiased iterative group registration template for cortical surface analysis. *Neuroimage*. 2007;34:1535–1544.
39. Chung MK, Worsley KJ, Robbins S, et al. Deformation-based surface morphometry applied to gray matter deformation. *Neuroimage*. 2003;18:198–213.
40. Kwak K, Yoon U, Lee D-K, et al. Fully-automated approach to hippocampus segmentation using a graph-cuts algorithm combined with atlas-based segmentation and morphological opening. *Magn Reson Imaging*. 2013;31:1190–1196.
41. Jack CR Jr, Wiste HJ, Weigand SD, et al. Age-specific and sex-specific prevalence of cerebral beta-amyloidosis, tauopathy, and neurodegeneration in cognitively unimpaired individuals aged 50-95 years: a cross-sectional study. *Lancet Neurol*. 2017;16: 435–444.
42. Kim J, Jahng S, Kim S, et al. A comparison of item characteristics and test information between the K-MMSE~ 2: SV and K-MMSE. *Dement Neurocogn Disord*. 2024;23:117.
43. Villeneuve S, Rabinovici GD, Cohn-Sheehy BI, et al. Existing Pittsburgh Compound-B positron emission tomography thresholds are too high: statistical and pathological evaluation. *Brain*. 2015;138:2020–2033.
44. Klunk WE, Koeppe RA, Price JC, et al. The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET. *Alzheimers Dement*. 2015;11:1–15; e11-14.
45. Cho SH, Choe YS, Kim HJ, et al. A new Centiloid method for (18)F-florbetaben and (18)F-flutemetamol PET without conversion to PiB. *Eur J Nucl Med Mol Imaging*. 2020;47: 1938–1948.
46. Jang H, Kim JS, Lee HJ, et al. Performance of the plasma Aβ42/Aβ40 ratio, measured with a novel HPLC-MS/MS method, as a biomarker of amyloid PET status in a DPUK-KOREAN cohort. *Alzheimers Res Ther*. 2021;13:1–13.
47. Kang Y, Na DL. *Seoul Neuropsychological Screening Battery (SNSB)*. Incheon: Human Brain Research & Consulting Co; 2003.
48. Burnham SC, Bourgeat P, Doré V, et al. Clinical and cognitive trajectories in cognitively healthy elderly individuals with suspected non-Alzheimer's disease pathophysiology (SNAP) or Alzheimer's disease pathology: a longitudinal study. *The Lancet Neurology*. 2016;15:1044–1053.
49. Ye BS, Seo SW, Kim CH, et al. Hippocampal and cortical atrophy in amyloid-negative mild cognitive impairments: comparison with amyloid-positive mild cognitive impairment. *Neurobiol Aging*. 2014;35:291–300.
50. Saridin FN, Chew KA, Reilhac A, et al. Cerebrovascular disease in suspected non-Alzheimer's pathophysiology and cognitive decline over time. *Eur J Neurol*. 2022;29:1922–1929.

51. Chui HC, Zarow C, Mack WJ, et al. Cognitive impact of subcortical vascular and Alzheimer's disease pathology. *Ann Neurol*. 2006;60:677–687.
52. Wisse L, Das S, Davatzikos C, et al. Defining SNAP by cross-sectional and longitudinal definitions of neurodegeneration. *Neuroimage Clin*. 2018;18:407–412.
53. Thal DR, Grinberg LT, Attems J. Vascular dementia: different forms of vessel disorders contribute to the development of dementia in the elderly brain. *Exp Gerontol*. 2012;47:816–824.
54. Wirth M, Villeneuve S, Haase CM, et al. Associations between Alzheimer disease biomarkers, neurodegeneration, and cognition in cognitively normal older people. *JAMA Neurol*. 2013;70:1512–1519.
55. Moon H, Ham H, Yun J, et al. Prediction of amyloid positivity in patients with subcortical vascular cognitive impairment. *J Alzheimers Dis*. 2024;99:1117–1127.
56. Strittmatter WJ, Saunders AM, Schmechel D, et al. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc Natl Acad Sci U S A*. 1993;90:1977–1981.
57. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*. 1993;261:921–923.
58. Wisse L, De Flores R, Xie L, et al. Pathological drivers of neurodegeneration in suspected non-Alzheimer's disease pathophysiology. *Alzheimers Res Ther*. 2021;13:100.
59. Crary JF, Trojanowski JQ, Schneider JA, et al. Primary age-related tauopathy (PART): a common pathology associated with human aging. *Acta Neuropathol*. 2014;128:755–766.
60. Jack CR Jr. PART and SNAP. *Acta Neuropathol*. 2014;128:773–776.
61. Roe CM, Fagan AM, Grant EA, et al. Amyloid imaging and CSF biomarkers in predicting cognitive impairment up to 7.5 years later. *Neurology*. 2013;80:1784–1791.
62. Lee MJ, Seo SW, Na DL, et al. Synergistic effects of ischemia and β-amyloid burden on cognitive decline in patients with subcortical vascular mild cognitive impairment. *JAMA psychiatry*. 2014;71:412–422.
63. Jang H, Kim HJ, Park S, et al. Application of an amyloid and tau classification system in subcortical vascular cognitive impairment patients. *Eur J Nucl Med Mol Imaging*. 2020;47:292–303.
64. Jang H, Kim HJ, Choe YS, et al. The impact of amyloid-β or tau on cognitive change in the presence of severe cerebrovascular disease. *J Alzheimers Dis*. 2020;78:573–585.
65. Chun MY, Jang H, Kim S-J, et al. Emerging role of vascular burden in AT (N) classification in individuals with Alzheimer's and concomitant cerebrovascular burdens. *J Neurol Neurosurg Psychiatry*. 2024;95:44–51.
66. Hughes TM, Wagenknecht LE, Craft S, et al. Arterial stiffness and dementia pathology: atherosclerosis Risk in Communities (ARIC)-PET Study. *Neurology*. 2018;90:e1248–e1256.
67. Nichols JB, Malek-Ahmadi M, Tariot PN, et al. Vascular lesions, APOE ε4, and tau pathology in Alzheimer disease. *J Neuropathol Exp Neurol*. 2021;80:240–246.
68. Lee P, Ryoo H, Park J, et al. Morphological and microstructural changes of the Hippocampus in early MCI: a study utilizing the Alzheimer's disease neuroimaging initiative database. *J Clin Neurol*. 2017;13:144–154.