DND Dementia and Neurocognitive Disorder

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Study Design and Baseline Results in a Cohort Study to Identify Predictors for the Clinical Progression to Mild Cognitive Impairment or Dementia From Subjective Cognitive Decline (CoSCo) Study

SeongHee Ho [ID],[1] Yun Jeong Hong [ID],[2] Jee Hyang Jeong [ID],[3] Kee Hyung Park [ID],[4] SangYun Kim [ID],[5,6] Min Jeong Wang [ID],[7] Seong Hye Choi [ID],[8] SeungHyun Han,[9] Dong Won Yang [ID] [1]

[1]Department of Neurology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[2]Department of Neurology, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Uijeongbu, Korea
[3]Department of Neurology, Ewha Womans University Seoul Hospital, Ewha Womans University School of Medicine, Seoul, Korea
[4]Department of Neurology, College of Medicine, Gachon University Gil Medical Center, Incheon, Korea
[5]Department of Neurology, Seoul National University College of Medicine, Seoul, Korea
[6]Clinical Neuroscience Center, Seoul National University Bundang Hospital, Seongnam, Korea
[7]ROA Neurology Clinic, Seongnam, Korea
[8]Department of Neurology, Inha University, School of Medicine, Incheon, Korea
[9]ROWAN Inc., Seoul, Korea

Correspondence to
Dong Won Yang
Department of Neurology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea.
Email: neuroman@catholic.ac.kr

ORCID iDs
SeongHee Ho [ID]
https://orcid.org/0000-0002-4419-9299
Yun Jeong Hong [ID]
https://orcid.org/0000-0002-4996-4981
Jee Hyang Jeong [ID]
https://orcid.org/0000-0001-7945-6956
Kee Hyung Park [ID]
https://orcid.org/0000-0001-6847-6679
SangYun Kim [ID]
https://orcid.org/0000-0002-9101-5704
Min Jeong Wang [ID]
https://orcid.org/0000-0001-7215-4883
Seong Hye Choi [ID]
https://orcid.org/0000-0002-0680-8364

ABSTRACT

Background and Purpose: Subjective cognitive decline (SCD) refers to the self-perception of cognitive decline with normal performance on objective neuropsychological tests. SCD, which is the first help-seeking stage and the last stage before the clinical disease stage, can be considered to be the most appropriate time for prevention and treatment. This study aimed to compare characteristics between the amyloid positive and amyloid negative groups of SCD patients.

Methods: A cohort study to identify predictors for the clinical progression to mild cognitive impairment (MCI) or dementia from subjective cognitive decline (CoSCo) study is a multicenter, prospective observational study conducted in the Republic of Korea. In total, 120 people aged 60 years or above who presented with a complaint of persistent cognitive decline were selected, and various risk factors were measured among these participants. Continuous variables were analyzed using the Wilcoxon rank-sum test, and categorical variables were analyzed using the χ^2 test or Fisher's exact test. Logistic regression models were used to assess the predictors of amyloid positivity.

Results: The multivariate logistic regression model indicated that amyloid positivity on PET was related to a lack of hypertension, atrophy of the left temporal lateral and entorhinal cortex, low body mass index, low waist circumference, less body and visceral fat, fast gait speed, and the presence of the apolipoprotein E ε4 allele in amnestic SCD patients.

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Dong Won Yang
https://orcid.org/0000-0002-4733-7298

Conclusions: The CoSCo study is still in progress, and the authors aim to identify the risk factors that are related to the progression of MCI or dementia in amnestic SCD patients through a two-year follow-up longitudinal study.

Keywords: Subjective Cognitive Decline; Risk Factors

INTRODUCTION

Subjective cognitive decline (SCD) refers to the self-perception of cognitive decline with normal performance on objective neuropsychological tests.[1] It encompasses a heterogeneous group that includes patients with varying degrees of cognitive dysfunction and various etiologies. SCD has been believed to be caused by anxiety and depression. However, previous longitudinal studies have revealed its tendency to develop into Alzheimer's disease (AD); as a result, it has recently come to be considered a part of the AD spectrum.[2] According to the 2011 National Institute on Aging and Alzheimer's Association, preclinical AD stage 3 is defined as SCD when there are biomarkers of amyloid accumulation and early neurodegeneration with evidence of subtle cognitive decline.[3] The risk of progression of preclinical AD stage 3 to mild cognitive impairment (MCI) or AD in 5 years is 34.2% and 10.7%, respectively.[4]

Recently, various disease-modifying drugs have been developed to slow the onset and progression of AD dementia; however, most drugs have failed except for aducanumab, which was approved by the Food and Drug Administration on June 7, 2021.[5] The most plausible explanation for these drug failures is that the starting time for AD therapies might be too late, as it is possible that most treatments start after substantial brain tissue injury has occurred.[6] Therefore, AD-related clinical studies are expected to begin at the preclinical stage in the future.[7] In other words, SCD—which is the first help-seeking stage and the last stage before the clinical disease stage—is the most appropriate time for prevention and treatment.

Human monoclonal antibodies that selectively bind to amyloid beta (Aβ) fibrils and soluble oligomers can decrease Aβ plaques in the brain. In attempting to reduce Aβ plaques using a monoclonal antibody in SCD, it is important to select appropriate subjects who might progress rapidly to MCI or dementia.

In SCD patients, the characteristics that are likely to contribute to progression to MCI or AD are explained by the concept of SCD plus.[1] SCD has the following features: subjective decline in memory rather than other cognitive domains, onset of SCD within the last 5 years, onset of SCD at 60 years and older, concerns associated with SCD, and feeling of performing worse than others within the same age group.[1] In our previous study, older age, lower Mini-Mental State Examination (MMSE) recall scores, apolipoprotein E (APOE) ε4 carriers, and lower verbal delayed recall scores were found to be the most relevant factors for the progression from subjective memory impairment to MCI or AD.[8] It takes a long time to switch to MCI or AD from SCD; thus, several patients need to be followed up with over a long period of time to identify risk factors. Therefore, this study was conducted by enrolling people who are likely to progress to MCI or AD rapidly, which shortened the follow-up period. This study aimed to identify the risk factors related to progression from SCD to MCI or dementia, and it is expected to contribute to the selection of SCD subjects at risk for disease-modifying drug studies. The study will further aid in the application of cognitive and physical activity

programs to reduce the progression of cognition or incidence of dementia. To this point, we have obtained baseline data, and this paper intended to demonstrate the characteristics related to florbetaben positron emission tomography (PET) positivity.

METHODS

Overall study design

A cohort study to identify predictors for the clinical progression to mild cognitive impairment or dementia from subjective cognitive decline (CoSCo) study is a multicenter, prospective observational study conducted in the Republic of Korea. The aim of this cohort study was to enroll 120 people aged 60 years or older who presented with a complaint of persistent cognitive decline in 6 different memory clinics. The assessments within the CoSCo study included clinical and neuropsychological examinations, blood sampling, body composite score using InBody (InBody H20®; InBody, Seoul, Korea), gait analysis, brain magnetic resonance imaging (MRI), F^{18}-florbetaben PET, blood-based amyloid quantification test, quantitative electroencephalography (EEG), pure tone audiometry (PTA), subjective perception questionnaire survey, and wearable device data evaluation at baseline. Clinical and neuropsychological examination, subjective perception questionnaire survey, body composite score, and gait analysis were checked annually. Wearable devices were worn every year to obtain annual measurements. Brain MRI, blood-based amyloid quantification test, quantitative EEG, and PTA were followed up after 2 years. Participants in CoSCo were followed up with annually, and the total study period was 3 years. The purpose of this study was to identify the early risk factors that can predict the progression to MCI or dementia by constructing a cohort of elderly patients with SCD. The first patient was enrolled in November 2018, and the last patient baseline data were obtained in November 2019. In total, 120 participants were enrolled and had their data analyzed in the baseline study.

All data were stored in a web-based clinical research management system and monitored centrally using a query process. The image data were stored centrally for further analysis. A standardized study protocol was established through regular research meetings that were held to achieve high-quality data and material acquisition. The study protocol was reviewed and approved by the Institutional Review Boards of each institution: The Catholic University of Korea, Seoul St. Mary's Hospital (KC18ONDI0394), Ewha Womans University Mokdong Hospital (EUMC2018-08-022-005), Gachon University Gil Medical Center (GAIRB2019-231), Seoul National University Bundang Hospital (B-1808/486-004), and Inha University School of Medicine (IN-HAUH2018-08-006-005). All participants provided informed consent, and the study was conducted in accordance with the Declaration of Helsinki.

Participants

In total, 120 people aged 60 years or older who presented with a complaint of persistent cognitive decline were prospectively enrolled in 6 different dementia centers or clinics: The Catholic University Seoul St. Mary's Hospital, Seoul National University Bundang Hospital, Ewha Womans University Mokdong Hospital, Inha University Hospital, Gachon University Gil Hospital, and ROA Neurology Clinic. None of the subjects met the dementia criteria in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders[9] or the MCI criteria by Petersen.[10] SCD patients have been defined as those at −1.5 standard deviations (SDs, 7th percentile) or higher on the neuropsychological test.[11] However, we selected the high-risk group that seemed to progress to MCI or dementia quickly in accordance with a previous

study.[8] Subjects over 60 years old who were in the range of the 7th to 50th percentiles (−1.5 SD ≤ z-score ≤ 0 SD) of the verbal memory domain and over the 7th percentile (−1.5 SD ≤ z-score) of the other domains were recruited through neuropsychological tests. Accordingly, people likely to progress rapidly based on a shortened follow-up period were selected and labeled as "amnestic SCD." All patients had graduated from elementary school or higher, and they duly provided informed consent. Those who had brain lesions and blood test abnormalities that affected cognitive functioning were excluded. Subjects with uncontrolled depression, schizophrenia, alcoholism, drug dependence, brain lesions, and blood abnormalities that may affect cognitive functioning were also excluded.

Clinical and risk factor assessments
Clinical assessments were performed at baseline and scheduled for annual follow-up assessments. The assessments included age, sex, education level, medical and family history, current medications, comorbidity, and lifestyle factors (e.g., smoking, alcohol, exercise). Vital signs such as blood pressure, pulse rate, height, and weight were obtained for the Framingham cardiovascular risk profile calculation. Blood chemistry tests (i.e., liver function test, blood sugar level, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, protein, syphilis, thyroid function test, vitamin B12, and folate), and testing for APOE genotype were performed. All patients underwent a hand grip strength test using a hand gripper (dynamometer, TKK-5401; TAKEI, Niigata, Japan), calf circumference measurement using a tape measure, body composite analysis using InBody (InBody H20®; InBody), measurement of balance (time required to stand with both feet, with both feet back and forth, and with a single foot), and lower extremity strength test (time required to stand and sit on a chair 5 times). Participants' hearing ability, physical activity, and sleeping pattern were evaluated using PTA and wearable devices (Fitbit Alta HR® & Fitbit Inspire HR®; Fitbit, Inc., San Francisco, CA, USA).

Neuropsychological evaluation
All participants received some of the tests listed in the Seoul Neuropsychological Screening Battery-2nd version (SNSB-II) for cognitive function evaluation[12]; these included the Digit-Span Test (forward), the Korean version of the Boston Naming Test, the Rey-Osterrieth Complex Figure Test (composed of copying as well as immediate and 20-minute-delayed recall), the Seoul Verbal Learning Test (SVLT; a 20-minute-delayed recall trial of 12 items), the Digit Symbol Coding test, the phonemic Controlled Oral Word Association Test (COWAT), the Korean-Trail Making Test-Elderly version: Part B time, and the Korean Color Word Stroop Test (color reading of 112 items over a 2-minute period). All test results were analyzed based on z-scores. The z-scores were standardized by age and educational criteria presented in the SNSB-II based on a large, nationwide Korean sample (1,100 people), thereby enabling comparisons with population averages. A z-score <0 indicates a poor performance relative to the population average, while a z-score <−1.5 SD indicates a severely poor performance. SCD patients were defined as those with a z-score of −1.5 SD or higher in all domains of the SNSB-II in order to exclude patients with MCI. In accordance with our previous study results, the present study only included those patients who seemed to develop MCI or dementia rapidly with SVLT delayed recall score between −1.5 SD and 0.[8] General cognition was assessed using the Korean version of the MMSE, called K-MMSE.

Acquisition of brain MRI and F[18]-florbetaben PET
Brain MRI included T1-weighted axial, T2-weighted, fluid-attenuated inversion recovery, and 3-dimensional (3D) T1 thin section images captured using a 3.0T MRI scanner. Imaging

acquisition conditions were maintained as described in the protocol outlined in the Alzheimer's Disease Neuroimaging Initiative study.[13] All follow-up brain MRI scans were acquired using the same brain MRI machine that was used for the first MRI acquisition under the same conditions. The presence or absence of structural lesions in the brain that could cause cognitive impairment was determined through readings by radiologists, which were double-checked by neurologists. Lacunes, microbleeds, white matter hyperintensities, and the degree of medial temporal atrophy according to the Scheltens visual rating scale[14] were evaluated by one neurologist. Brain volume was measured based on 3D T1 MRI using Quick Brain Volumetry (QBraVo), an automated analysis program developed for brain volumetry, and previously validated with a manual measurement.[15] QBraVo conducted imaging normalization on the template, segmentation by the tissue classes, and the regional division and calculation of brain volume. Gray and white matter volumes and their ratios to total brain were analyzed in 26 anatomical subdivisions and specific regions, including the hippocampus, entorhinal cortex, and ventricle. All participants underwent florbetaben PET at baseline. The existing PET data were used for analysis when the florbetaben PET was performed within one year from the baseline. Amyloid PET positivity was determined using the visual rating brain amyloid plaque load score[16] as obtained by a trained nuclear medicine specialist in a participating hospital. Moreover, MATLAB version 2013a and SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8) were used to obtain the quantitative regional amyloid burden. Individual 3D T1-weighted MRI scans were pre-processed, estimated, and co-registered into the corresponding PET images. Individual MR images were normalized into a standardized stereotaxic space and divided into 3 probabilistic tissue maps composed of gray matter, white matter, and cerebrospinal fluid. A volume-based template with 90 regions of interest (ROIs), named automated anatomical labeling, was aligned to the individual MRI. The standardized uptake value ratio (SUVR) was obtained using whole voxels of florbetaben PET images based on uptake in the cerebellar gray matter, which was set as a reference region. Global SUVR was calculated as the average of 90 regional uptake values.

Quantitative EEG

EEG was measured at 19 channels of the international 10–20 system with the participants' eyes opened for 3 minutes and closed for 3 minutes. These data were converted into a linked ear reference and stored in edf format files without filtering (if edf data must be stored in the filtered format, then the raw EEG data should be high-pass filtered offline from below 1 Hz and low-pass filtered offline toward above 45 Hz). Band pass filtering was applied to the EEG data with a passband from 1.0 to 45.0 Hz, and transient noisy epoch rejection was applied to improve the independent component analysis (ICA) performance. Then, adaptive mixture independent component analysis (amICA) was used to remove stationary artifacts such as ECG and electromyography artifacts.[17] With the cleaned EEG data, sensor-level analysis using a spectopo function based on EEGLAB[18] was performed in the following 8 spectral bands: delta (1–4 Hz), theta (4–8 Hz), alpha1 (8–10 Hz), alpha2 (10–12 Hz), beta1 (12–15 Hz), beta2 (15–20 Hz), beta3 (20–30 Hz), and gamma (30–45 Hz). Source cortical activity was mathematically estimated using standardized low-resolution brain electromagnetic tomography.[19] Source-level power was calculated at the voxel level and segmented into 68 ROIs using the Desikan-Killiany atlas.[20] The source-level connectivity between 68 ROIs was calculated using imaginary coherence.[21] The default mode network activity was also extracted from the connectivity matrix. All pre-processing steps, de-noising using amICA, sensor-level feature extractions, and source-level feature extractions were performed on iSyncBrain® (Seoul, Korea).

Blood Aβ oligomerization

Aβ oligomerization in plasma can be measured using a Multimer Detection System-Oligomeric Aβ (MDS-OAβ). The inBloodTM™ OAβ test (People Bio Inc., Seongnam, Korea) was used to quantify MDS-OAβ values in an ethylenediamine tetra-acetic acid vacutainer tube. The detailed protocol has been described in a previous study.[22]

Gait analysis

Gait speed was measured by having each participant walk 7 m as quickly as possible. All participants walked twice so that an average time could be calculated. After measuring the average usual walking speed, gait analysis paired with a mental task was performed. In this test, the patients walked 7 m paired with a phonemic COWAT test. They walked while speaking a word starting with the Korean letter "ㅇ" followed by a word starting with the Korean letter "ㅅ". The average walking time was used to evaluate gait with mental tasks.

Wearable device

Wearable devices were distributed using separate firmware. Commercially available Fitbit Alta HR® & Fitbit Inspire HR® (Fitbit) were used to obtain the necessary biometric information, and the software was developed by ROWAN Inc. (Seoul, Korea). Biometric information (the amount and intensity of exercise, the speed and amount of walking, the amount and pattern of sleep, etc.) was measured in real time for 2 weeks every year. The biometric information collected from the wearable device was transmitted to a cloud server and then to the main server, where it was visualized (graphed) for accessibility to medical staff and guardians.

Questionnaires

All participants completed the following questionnaires: Korean-everyday cognition[23] to evaluate self-rated cognitive ability; the Korean Hearing Handicap Inventory for the Elderly (K-HHIE)[24] to evaluate hearing impairment; and the Patient Health Questionnaire-9[25] to evaluate depression severity. Further, the Brief Encounter Psychosocial Instrument[26] was used for stress measurement whereas the Pittsburgh Sleep Quality Index[27] was used for sleep quality.

Statistical analyses

The variables of interest were as follows: demographics, presence of medical comorbid conditions, family history of dementia, APOE genotype, neuropsychological tests, self-rated questionnaires, regional or whole volume of brain-by-brain MRI, amyloid PET, SUVR, visual reading, blood-based amyloid biomarker, gait analysis, and biometric information acquired by wearable devices. Continuous variables were analyzed using the Wilcoxon rank-sum test, and categorical variables were analyzed using the χ^2 test or Fisher's exact test. Logistic regression models were used to assess the predictors of amyloid positivity. Univariate regression models were used to analyze the variables of interest. The significant predictors identified through the univariate logistic regression models were used as independent variables in the multivariate logistic regression analysis. All analyses were performed using SPSS version 24 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at $p<0.05$.

RESULTS

In total, 120 patients with SCD were enrolled in the CoSCo study, which was designed as a longitudinal study intended to determine the risk factors affecting the progression to MCI or dementia among SCD patients. However, only baseline data could be obtained at the time of

documenting this study, as follow-up studies have yet to be completed. The main purpose of this study was to demonstrate the characteristics related to florbetaben PET positivity based on visual rating, which has been considered to be highly predictive for rapid conversion to MCI or dementia.

Of the 120 SCD patients, 53 were male (44.2%) and 67 were female (55.8%). The mean age of SCD participants was 70.8 years, and the mean amount of education was 11.2 years. Twenty-six (21.7%) patients presented with amyloid PET positivity. The basic demographics and clinical characteristics are presented in **Table 1**. SCD patients with positive amyloid PET had a higher proportion of APOE ε4 carriers (46.2%) than those with negative amyloid PET SCD (12.8%). Compared to the amyloid PET negative group, the amyloid PET positive group was older (73.8±5.6 vs. 70.0±6.0) and included a higher proportion of males (61.5% vs. 39.5%). Amnestic SCD patients with amyloid PET positivity had more years of education (12.3±4.1 vs. 10.8±4.0) than those in the negative group. Basic demographics, such as medical and family history and lifestyle factors, were not significantly different between the 2 groups, aside from history of hypertension and angina. The SUVR analysis of amyloid PET positive

Table 1. Demographic features of the CoSCo study population

Characteristics	Overall (n=120)	Amyloid PET (−) (n=94)	Amyloid PET (+) (n=26)	*p*-value
Age (yr)	70.8±6.1	70.0±6.0	73.8±5.6	0.007
Sex, female	67 (55.8)	57 (60.6)	10 (38.5)	0.038
Education (yr)	11.2±4.1	10.8±4.0	12.3±4.1	0.086
APOE ε4 carrier (yes)	24 (20.0)	12 (12.8)	12 (46.2)	<0.001
Family history (yes)	43 (35.8)	34 (36.2)	9 (34.6)	0.855
Hypertension (yes)	53 (44.2)	46 (48.9)	7 (26.9)	0.041
DM (yes)	33 (27.5)	27 (28.7)	6 (23.1)	0.549
Dyslipidemia (yes)	51 (42.5)	44 (46.8)	7 (26.9)	0.063
CAD (yes)	4 (3.3)	1 (1.1)	3 (11.5)	0.032
Smoking (yes)	3 (2.5)	2 (2.1)	1 (3.8)	0.260
Alcohol (yes)	44 (36.7)	35 (37.2)	9 (34.6)	0.778
Global SUVR	1.3±0.2	1.2±0.1	1.6±0.3	<0.001
MDS-OAβ (ng/mL)	1.0±0.2	1.0±0.2	1.0±0.1	0.163
TC (mg/dL)	174.8±34.9	172.3±35.4	183.7±32.0	0.077
HDL cholesterol (mg/dL)	55.6±14.5	54.9±14.2	58.3±15.2	0.387
PTA (dB)	26.8±15.2	25.2±14.9	32.4±15.3	0.032
BMI	24.8±3.2	25.3±3.1	23.0±2.7	0.002
Waist circumference (cm)	86.2±9.3	87.5±9.1	81.6±8.7	0.006
Body fat calculator (%)	29.1±7.9	30.1±7.6	25.6±8.0	0.011
Visceral fat	9.1±3.8	9.8±3.7	6.8±2.8	<0.001
Hand grip strength (kg)	38.7±21.5	37.6±20.1	42.8±26.2	0.351
Calf circumference (cm)	34.5±2.8	34.6±2.8	34.3±2.6	0.653
Standing with both feet (sec)	9.4±1.6	9.3±1.7	9.8±1.0	0.160
Standing with both feet back and forth (sec)	9.2±1.8	9.1±1.9	9.6±1.3	0.350
Standing with one foot (sec)	8.7±2.1	8.6±2.2	9.2±1.8	0.128
Lower extremity strength (sec)	9.9±3.1	10.1±3.3	9.3±2.5	0.317
Gait speed (sec)	5.9±1.6	6.0±1.6	5.2±1.4	0.008
Gait speed with mental task (sec)	8.2±3.7	8.5±4.0	7.2±2.0	0.139
Korean-everyday cognition	70.5±21.7	70.8±21.8	69.6±22.0	0.972
K-HHIE	6.9±13.1	5.5±12.1	11.8±15.4	0.006
PHQ-9	2.9±3.7	3.1±3.9	2.4±2.9	0.443
BEPSI	7.8±3.6	7.9±3.6	7.3±3.4	0.367
PSQI	5.8±3.6	5.9±3.6	5.7±3.5	0.776

Values are numbers (percentages) for categorical variables or mean ± standard deviation. The *p*-values were determined by the χ^2 test, Fisher's exact test, or the Wilcoxon rank sum test.
CoSCo: cohort study to identify predictors for the clinical progression to mild cognitive impairment or dementia from subjective cognitive decline, PET: positron emission tomography, APOE: apolipoprotein E, DM: diabetes mellitus, CAD: coronary artery disease, SUVR: standardized uptake value ratio, MDS-OAβ: Multimer Detection System-Oligomeric Aβ, TC: total cholesterol, HDL: high density lipoprotein, PTA: pure tone audiometry, BMI: body mass index, K-HHIE: Korean Hearing Handicap Inventory for the Elderly, PHQ-9: Patient Health Questionnaire-9, BEPSI: Brief Encounter Psychosocial Instrument, PSQI: Pittsburgh Sleep Quality Index.

SCD patients showed higher values than those of PET negative SCD patients (1.6% vs. 1.2%). Those with positive amyloid PET and SCD also had slightly higher blood amyloid positivity (61.5%) than those with negative amyloid PET and SCD (44.6%), although this finding was not statistically significant. Amyloid PET-positive SCD participants had a lower body mass index (BMI) and higher severity of hearing loss than amyloid PET-negative participants. The results of the hand grip strength test, calf circumference, measurement of balance, lower extremity strength test, and gait speed with mental task were not significantly different between the 2 groups. There were no statistically significant differences between the 2 groups in the questionnaires.

There was no statistically significant difference in the z-scores of the neuropsychological tests between the 2 groups, but the overall scores were low in the amyloid PET-positive group (**Table 2**). As presented in **Table 3**, the amyloid PET-positive SCD group had a lower regional brain volume ratio in the frontal (dorsolateral and inferior), temporal (anterior, medial, and

Table 2. Neuropsychological test in subjective cognitive decline patients with amyloid positive scan and amyloid negative scan

Characteristics	Overall (n=120)	Amyloid PET (−) (n=94)	Amyloid PET (+) (n=26)	*p*-value
DST:F (z-score)	0.6±1.1	0.6±1.1	0.5±1.2	0.516
K-BNT (z-score)	0.4±1.0	0.5±1.0	0.2±1.1	0.293
RCFT-copy (z-score)	0.2±0.6	0.2±0.6	0.3±0.6	0.520
SVLT-E: delayed recall (z-score)	−0.7±0.5	−0.6±0.5	−0.8±0.5	0.113
RCFT: delayed recall (z-score)	0.0±0.8	0.0±0.8	−0.1±0.9	0.238
DSC (z-score)	0.5±1.0	0.6±1.0	0.1±1.1	0.137
COWAT (z-score)	0.2±1.0	0.2±0.9	0.3±1.3	0.997
K-TMT-E:B (z-score)	0.3±0.6	0.4±0.6	0.2±0.7	0.224
K-CWST:CR (z-score)	0.1±0.8	0.2±0.8	−0.1±0.9	0.287
Total MMSE score	27.2±2.0	27.4±1.9	26.8±2.3	0.282

Values are mean ± standard deviation. The *p*-values were determined by the χ^2 test, Fisher's exact test, or the Wilcoxon rank sum test.
PET: positron emission tomography, DST:F: Digit-Span Test: Forward, K-BNT: Korean version of the Boston Naming Test, RCFT: Rey-Osterrieth Complex Figure Test, SVLT-E: Seoul Verbal Learning Test-Elderly, DSC: digit symbol coding, COWAT: Controlled Oral Word Association Test; K-TMT-E:B: Korean-Trail Making Test-Elderly: B, K-CWST:CR: Korean Color Word Stroop Test: Color Reading, MMSE: Mini-Mental State Examination.

Table 3. Neuroimaging characteristics of subjective cognitive decline subjects according to amyloid PET negativity or positivity on visual rating

Characteristics	Overall (n=120)	Amyloid PET (−) (n=94)	Amyloid PET (+) (n=26)	*p*-value
Frontal anterior lobe (%)	3.8±0.2	3.8±0.3	3.8±0.2	0.678
Frontal anterior medial lobe (%)	5.8±0.3	5.8±0.3	5.8±0.3	0.348
Frontal dorsolateral lobe (%)	5.1±0.3	5.1±0.3	5.0±0.2	0.038
Frontal inferior lobe (%)	4.4±0.3	4.4±0.3	4.3±0.2	0.020
Frontal posterior medial lobe (%)	4.1±0.2	4.1±0.2	4.1±0.2	0.702
Orbitofrontal lobe (%)	2.4±0.2	2.4±0.2	2.4±0.2	0.745
Temporal anterior lobe (%)	2.3±0.2	2.3±0.2	2.2±0.2	0.010
Temporal medial lobe (%)	2.3±0.2	2.4±0.1	2.3±0.2	0.001
Temporal lateral lobe (%)	10.1±0.5	10.2±0.5	9.8±0.5	0.002
Parietal lateral lobe (%)	9.1±0.6	9.2±0.6	8.8±0.4	0.005
Parietal medial lobe (%)	5.1±0.3	5.1±0.3	5.1±0.3	0.487
Occipital lobe (%)	10.3±0.5	10.4±0.5	10.2±0.5	0.088
Central lobe (%)	9.2±0.5	9.3±0.5	8.9±0.4	<0.001
Cerebellum (%)	11.2±0.8	11.3±0.8	11.1±0.7	0.268
Ventricle (%)	5.3±1.6	5.1±1.6	6.0±1.3	0.005
Brain (%)	85.3±3.3	85.8±3.3	83.8±2.7	0.004
Total intracranial volume (cm³)	1,353.6±122.2	1,345.4±120.7	1,382.5±125.3	0.178
Lt. entorhinal cortex (%)	0.0017±0.0002	0.0017±0.0002	0.0016±0.0002	0.009
Rt. entorhinal cortex (%)	0.0015±0.0002	0.0015±0.0002	0.0014±0.0002	0.028
Lt. hippocampus (%)	0.0024±0.0003	0.0024±0.0003	0.0023±0.0003	0.047
Rt. hippocampus (%)	0.0024±0.0002	0.0025±0.0002	0.0024±0.0002	0.061

Unless otherwise indicated, values are numbers (percentages) for categorical variables. The *p*-values were determined by the χ^2 test, Fisher's exact test, or the Wilcoxon rank sum test.
PET: positron emission tomography, Lt.: left, Rt.: right.

lateral), parietal lateral, and entorhinal cortices. The amnestic SCD group with florbetaben PET positivity presented decreased alpha and increased delta powers in resting EEG, which are consistent with the reported results in patients with amnestic MCI or Alzheimer's dementia. Further details on EEG will be published in another paper. The wearable device was worn once; only data pertaining to 78 out of 120 patients could be obtained due to a lack of time for analysis, so these data were excluded from the study analysis. The data obtained from wearable devices will be reported in another paper.

In a multivariate logistic regression model (**Table 4**), lack of hypertension (adjusted odds ratio [OR], 0.33; 95% confidence interval [CI], 0.12–0.90; p=0.03) and atrophy of the cerebellum (adjusted OR, 0.50; 95% CI, 0.28–0.88; p=0.017), left temporal lateral (adjusted OR, 0.52; 95% CI, 0.29–0.94; p=0.031), and left entorhinal cortices (adjusted OR, 0.61; 95% CI, 0.38–0.98; p=0.042) were associated with a higher risk of amyloid PET positivity. Moreover, people with low BMI (adjusted OR, 0.46; 95% CI, 0.26–0.80; p=0.006) and less visceral (adjusted OR, 0.38; 95% CI, 0.21–0.70; p=0.002) and body (adjusted OR, 0.57; 95% CI, 0.35–0.92; p=0.02) fat had a higher risk of amyloid PET positivity. As has been shown in previous studies, APOE ε4 carriers (adjusted OR, 6.49; 95% CI, 2.26–18.66; p=0.001) were identified as the most potent factors in predicting amyloid positivity.

DISCUSSION

This study described the protocol of the SCD cohort, the CoSCo study, and the results of the 120 baseline datasets. The primary endpoint of this cohort study was to identify the predictors of clinical progression to mild cognitive impairment or dementia from SCD, which encompasses a heterogeneous group with various causes. However, recent studies have considered SCD as the preclinical stage of the AD spectrum. A previous study found that the most important variables for conversion from SCD to MCI or dementia were older age, lower MMSE recall scores, APOE ε4 carriers, and lower verbal delayed recall scores.[8] Based on the results of this study, only patients over 60 years of age with "amnestic SCD" were included. "Amnestic SCD" was defined as normal cognition with verbal memory scores ranging from the 7th to 50th percentiles. Compared to SCD patients with high memory scores, patients with amnestic SCD are expected to progress to MCI or dementia quickly, and to commonly present with AD pathology, due to the memory domain that can be damaged in early-stage AD. Since only baseline data have been obtained to this point, we identified characteristics

Table 4. Linear regression models evaluating the association between amyloid positron emission tomography positivity and risk factors

Variables	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p-value	Age adjusted OR (95% CI)	p-value
Age	1.89 (1.21–3.05)	0.007		
Hypertension	0.33 (0.12–0.90)	0.052	0.33 (0.12–0.90)	0.030
Lt. temporal lateral lobe (%)	0.52 (0.29–0.94)	0.001	0.52 (0.29–0.94)	0.031
Cerebellum (%)	0.43 (0.25–0.69)	0.001	0.50 (0.28–0.88)	0.017
Lt. entorhinal cortex (%)	0.61 (0.38–0.98)	0.009	0.61 (0.38–0.98)	0.042
BMI	0.46 (0.26–0.80)	0.003	0.46 (0.26–0.80)	0.006
Waist circumference (cm)	0.49 (0.29–0.79)	0.006	0.46 (0.27–0.79)	0.005
Body fat calculator (%)	0.56 (0.35–0.88)	0.014	0.57 (0.35–0.92)	0.020
Visceral fat	0.37 (0.19–0.64)	0.001	0.38 (0.21–0.70)	0.002
Gait speed (sec)	0.53 (0.27–0.91)	0.037	0.53 (0.29–0.95)	0.034
APOE ε4 genotype	5.62 (2.12–14.94)	0.001	6.49 (2.26–18.66)	0.001

Lt.: left, BMI: body mass index, APOE: apolipoprotein E, OR: odds ratio, CI: confidence interval.

of amyloid positive and amyloid negative groups in amnestic SCD patients. The prevalence of amyloid PET positivity in individuals with SCD ranges from approximately 12% to 43%.[28] In this study, the prevalence of amyloid PET positivity was 21.8%, and it was found to be relatively high in patients with SCD. A previous study showed greater amyloid PET positivity in APOE ε4 carriers than in APOE ε4 non-carriers.[29] Similarly, in our study, APOE ε4 carriers showed a higher rate of amyloid PET positivity than APOE ε4 non-carriers (46.2% vs. 12.8%). Recent studies have found that amyloid biomarkers are more likely to increase the risk of dementia in patients with SCD than tau or neurodegeneration biomarkers.[30] Therefore, the prominent features in amnestic SCD patients with amyloid pathology were investigated.

In this study, a multivariate logistic regression model showed that amyloid PET positivity was related to a lack of hypertension, atrophy of the left temporal, lateral and entorhinal cortex, low BMI, low waist circumference, less body and visceral fat, fast gait speed, and presence of the APOE ε4 allele in amnestic SCD patients.

Patients who were positive for amyloid PET had a lower rate of hypertension. Hypertension is a known risk factor for dementia in middle-aged individuals, and it is known to accelerate cognitive deterioration in AD through cerebrovascular damage. However, hypotension is believed to decrease cognitive function late in life.[31] Since the majority of SCD patients enrolled in our study were over 70 years old, we assumed that people with amyloid PET positive would have lower BP than those with amyloid PET negative. AD, which involves accumulated amyloid plaque in a brain, could reduce body mass index, thus resulting in a lower blood pressure.[32] We also interpreted our results to show that cognitive dysfunction in SCD patients with amyloid PET negativity is more related to vascular damage than it is in SCD patients with amyloid PET positivity. There were no differences in the size of lacunes or white matter hyperintensities, which are considered to be markers of vascular damage; however, it is difficult to accurately evaluate the degree of vascular damage without pathologic confirmation. Vascular dementia is more affected by cardiovascular diseases such as hypertension than Alzheimer's dementia.[33] The number of patients having both amyloid PET positivity and hypertension was 7, which was too small for analysis.

Previous studies reported that, among the SCD group, the amyloid PET-positive subgroup had more severe cognitive decline than the amyloid PET-negative subgroup.[34,35] In this study, there was no cognitive function difference between amyloid PET-positive and -negative groups, likely because only people who belonged to the 7th through 50th percentiles in the memory domain were selected. In some cognitive domains, there were lower scores in the amyloid PET-positive group, but this difference was not statistically significant. Another hypothesis is that the number of SCD patients with amyloid PET positivity was too small to be statistically significant.

Amnestic SCD patients with AD pathology showed atrophy in the entorhinal cortex and the temporal cortex, which are regions related to the memory domain. The entorhinal cortex and the temporal cortex are altered earlier in AD[36,37]; therefore, those with atrophy involving the entorhinal and temporal cortices are expected to show rapid cognitive worsening in the future. A previous volumetry study also showed a similar atrophy pattern in both amnestic MCI and SCD patients compared to normal control patients. Amnestic MCI and SCD groups showed atrophy in the bilateral hippocampus, amygdala, frontal lobe, occipital lobe, temporal lobe, cingulate lobe, and insular region.[38] This study also reported atrophy in the temporal and entorhinal cortices, which is consistent with the findings of previous studies.

Several studies have shown mixed results regarding the relationship between BMI and cognitive function. Being overweight or obese in middle age has been shown to increase the risk of dementia in late life through mechanisms such as hyperinsulinemia, advanced glycosylation products, adipocyte-derived hormones (adipokines and cytokines), and the influence of adiposity on vascular risk and cerebrovascular disease.[39] By contrast, some review studies have reported that the risk of dementia is increased not only by being overweight and obese but also by being underweight.[40] The relationship between BMI and cognitive decline in people with normal cognitive function is unclear; however, people with low baseline BMI show more rapid cognitive decline among people with MCI. In this study, amnestic SCD patients with a low BMI had a higher rate of amyloid PET positivity, which was similar to that in patients with MCI. Further, low body mass index, low waist circumference, and less body and visceral fat might be related to a low amount of muscle. In several meta-analyses, sarcopenia is highly correlated with cognitive impairment and has an OR of 2.25 in cognitive impairment for patients with sarcopenia compared to patients without sarcopenia.[41,42] However, there were no significant finding in hand grip strength and calf circumference, which we used to check muscle power and muscle mass in a baseline study. Subsequent studies should investigate whether changes in body fat or muscle mass can affect cognitive decline. Plasma Aβ is a promising diagnostic tool because of its cost-effectiveness and ease of accessibility. Previous studies have directly measured plasma Aβ oligomers, but an accurate measurement method has yet to be developed.[43,44] To measure oligomerization tendency, we used the method that was used by Youn et al.[22] The sensitivity and specificity of peripheral blood amyloid levels were high in cases of AD, which distinguished them from normal controls. Blood amyloid oligomerization tendency was higher but statistically insignificant in the amyloid PET-positive SCD group. Amyloid PET could be negative if an insufficient amount of amyloid plaque was accumulated or diffusely accumulated. Changes in blood amyloid oligomerization tendency could occur even before amyloid plaques accumulate in the brain, and examining the change in the blood amyloid oligomerization tendency through a longitudinal follow-up study might be helpful for the prediction of brain amyloid PET positivity or clinical progression. EEG is an easily accessible and non-invasive tool that can be used to evaluate of brain function. In previous studies, increased power at low frequencies (e.g., δ- and θ-bands) and decreased power at higher frequencies (α- and β-bands) were observed in AD and MCI patients.[45] In this study, SCD patients with amyloid PET positivity showed an EEG pattern similar to that seen in MCI. More detailed EEG results will be discussed in another paper.

In general, gait is slower in people with dementia or MCI than it is in those with normal cognition. However, the current study revealed a slower gait speed in SCD patients with amyloid PET negativity. Even people with normal cognition and slow gait velocity show poor cognitive function.[46] The results of this study were inconsistent with those that have previously been reported in the literature, and it is difficult to explain these discrepancies at this point. Therefore, it is necessary for follow-up research to determine whether gait speed in people with amyloid PET positivity or those who convert to MCI or dementia worsens faster.

Hearing loss is a well-known risk factor associated with cognitive decline.[47] In this study, SCD patients with amyloid PET positivity had a higher K-HHIE score than those with amyloid PET negativity. However, these data were excluded in the multivariable analysis for the prediction of amyloid PET positivity due to age differences between the 2 groups.

As of this writing, the CoSCo study is still in progress, with the goal of identifying the risk factors that are related to the progression of MCI or dementia in amnestic SCD patients

through a 2-year follow-up longitudinal study. Only baseline data were collected at this time point, and features related to amyloid PET positivity could be examined. After the follow-up period, subjects who progress to MCI or dementia will be categorized and risk factors contributing to clinical progression will be identified. The effect of amyloid PET positivity on the clinical progression will also be confirmed.

This study was supported by the Korea Health Industry Development Institute for 3 years. The 3-year study duration was too short to detect noticeable changes because of the small sample size and very slow clinical progression of SCD subjects, which represents a limitation of this study. Further plans for this research include the addition of 80 more SCD patients and extending the follow-up period by 3 years. The inclusion of sufficient conversion cases in an extension study is expected to allow for risk factors related to the progression from amnestic SCD to MCI or dementia to be identified. Another limitation is that subjects with normal cognition and SCD patients with memory domain scores over the 50th percentile were not included for comparison. A strength of this study is the inclusion of multi-modal monitoring of risk factors such as blood tests, body composite score using InBody, gait analysis, brain MRI, F^{18}-florbetaben PET, blood-based amyloid quantification test, quantitative EEG, PTA, subjective perception questionnaire survey, and wearable devices to obtain physiological data. Both central and peripheral amyloid pathology were examined to elucidate the clinical significance of blood amyloid biomarkers in the very early stages of the AD continuum and their relationship with central amyloid burden. This study is expected to be a helpful cohort study for identifying risk factors related to the progression from SCD to MCI or dementia.

Our study is exploratory research, and follow-up studies are needed to determine whether these risk factors can be generalized to more patients with SCD. In recent years, many AD treatments have failed in the MCI stage; hence, there is growing interest in the treatment of AD in the preclinical stage. Moreover, SCD is a heterogeneous group; therefore, the enrollment of SCD patients with risk factors for progression will be needed to further explore anti-amyloid therapies. It is also necessary to study whether controlling the risk factors will have a preventive effect on the progression to MCI or dementia.

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