Subtle Cognitive Deficits Are Associated with Amyloid-β Positivity, but Not Severity of Self-Reported Decline: Results from the CoSCo Study

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Keywords
Subjective cognitive decline · Subtle cognitive impairment · Amyloid-β · Alzheimer’s disease

Abstract
Introduction: Subjective cognitive decline (SCD) can be considered as the preclinical manifestation of Alzheimer’s disease (AD). The National Institute on Aging and the Alzheimer’s Association criteria for preclinical AD proposed that subtle cognitive changes appear along with AD biomarkers in the late stage of preclinical AD. The objective of this study was to explore whether subtle cognitive impairment (SCI) in individuals with SCD is associated with brain amyloid-β (Aβ) status and SCD severity. Methods: One hundred twenty individuals with SCD (mean age: 70.87 ± 6.10 years) were included in this study. SCI was defined as performance ≤ −1.0 SD on at least two neuropsychological tests. Participants underwent an amyloid positron emission tomography, which was assessed visually and quantitatively using standardized uptake value ratio (SUVR). The severity of SCD was assessed using two self-reported questionnaires: the SCD questionnaire based on the SCD-plus features and the Korean-Everyday Cognition (K-ECog) scale. Results: SCD individuals with SCI (n = 25) had more Aβ positivity than the SCD only group (n = 95) (44% vs. 15.79%; p = 0.002). In addition, the SCI group had a higher global SUVR than the SCD only group (p = 0.048). For self-reported questionnaires, there were no differences in SCD questionnaire total scores and K-ECog global and cognitive domain-specific scores between two groups. Conclusions: In SCD individuals, SCI was associated with higher Aβ positivity, but not with the severity of self-reported cognitive decline, compared to the SCD only group. These results suggest that the recognition of objectively defined subtle cognitive deficits may contribute to the early identification of AD in SCD.

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Introduction

Subjective cognitive decline (SCD) is defined by complaints of persistent cognitive decline with normal cognitive performance [1, 2]. SCD is related to an increased risk of cognitive decline and Alzheimer’s disease (AD) dementia and biomarker abnormalities for AD. Therefore, SCD in cognitively unimpaired older individuals can be considered a preclinical stage of AD [1].

After the presentation of preclinical AD criteria by the National Institute on Aging–Alzheimer’s Association (NIA-AA) [3], the concept of “subtle cognitive decline” was introduced. The NIA-AA criteria of preclinical AD consist of three stages depending on AD biomarkers and subjective cognitive decline. Although subjective cognitive decline corresponding to stage 3 of preclinical AD by the NIA-AA criteria is referred to by various terms such as subjective cognitive change, subjective cognitive impairment (SCI), objectively defined subtle cognitive difficulties, and pre-mild cognitive impairment (MCI) [4–9] and has yet to be definitively operationalized, it may represent the first detectable cognitive impairment in AD. Subjective cognitive decline can both be or not be accompanied by SCI (i.e., subjective cognitive complaints) in cognitively unimpaired older adults [5, 10]. Therefore, it is important to examine the clinical relevance of subjective cognitive decline along with SCD. Recent studies have specifically investigated subtle cognitive decline [8, 11–14]. However, few studies have focused on subtle cognitive deficits in SCD [15]. The aim of this study was to determine whether SCI in individuals with SCD is associated with brain amyloid-β (Aβ) status and the severity of SCD using the cohort study to identify predictors for the clinical progression to MCI or dementia from SCD (CoSCo).

Materials and Methods

Participants

The present study is a part of the CoSCo study which is a multicenter, prospective observational study. One hundred twenty people aged 60 years or older (53 men, 67 women), with six or more years of education, were enrolled from six memory clinics in the Republic of Korea between November 2018 and November 2019. The participants underwent detailed neuropsychological tests, brain MRI, laboratory tests including apolipoprotein E (APOE) genotyping, and 18F-florbetaben brain Aβ positron emission tomography (PET).

SCD was defined based on the research criteria for SCD [1]: (1) complaining of persistent cognitive decline; (2) cognitive test scores ≥7th percentile of age- and education-adjusted norms on all subtests of a neuropsychological test battery; (2–1) in addition, we recruited SCD subjects between the 7th percentile and 50th percentile on verbal memory test to include SCD individuals with higher risk who may progress to MCI or AD dementia [16]; (3) criteria for MCI based on Petersen’s criteria [17] or dementia according to the Diagnostic and Statistical Manual of Mental Disorders V criteria [18] were not met. Participants were excluded if they had significant neurologic illnesses, major psychiatric disorders, or abnormal laboratory findings that affect cognitive function.

The study was approved by the Institutional Review Boards of each institution. All participants provided informed consent, and the study was conducted in accordance with the Declaration of Helsinki.

Neuropsychological Test

All participants completed the Korean version of the Mini-Mental State Examination (K-MMSE) [19] and detailed neuropsychological tests [20]. Neuropsychological testing included the following: (1) attention – Forward Digit Span Test; (2) language – the Korean version of the Boston Naming Test; (3) visuospatial function – the Rey Complex Figure Test (RCFT); (4) memory – the Seoul Verbal Learning Test (SVLT) delayed recall and RCFT delayed recall; and (5) frontal executive function – the Digit Symbol Coding, the Controlled Oral Word Association Test (COWAT) (phonemic), Trail Making Test-B, and the Stroop Test (color reading).

While subtle cognitive decline has yet to be definitively operationalized, the SCI in the present study was defined by adapting the method used in previous studies [10, 21]: cognitive performance of >1.0 SD below the normative mean on at least two out of the nine neuropsychological tests. The Patient Health Questionnaire-9 (PHQ-9) was used to measure participants’ depressive symptoms [22, 23]. The scores range from 0 to 27, with higher scores indicating more depressive symptoms. The Korean version of the Brief Encounter Psychosocial Instrument (BEPSI-K) [24], a modified version of the original BEPSI [25], was used to assess stress levels. The scores range from 1 to 5, with a higher score indicating a higher level of stress.

Assessment of SCD

The severity of SCD was assessed using two self-reported questionnaires: the SCD questionnaire based on the SCD-plus features and the Korean-Everyday Cognition (K-ECog) scale. The SCD questionnaire with 10 questions [26] based on the SCD-plus features that increase the likelihood of preclinical AD, as described by the SCD Initiative Working Group [1], was applied to assess subjective cognitive complaints. Table 1 shows items included in the SCD questionnaire and rating. The total of SCD questionnaire ranged from 0 to 29, with higher scores indicating greater perceived cognitive decline.

The 39-item K-ECog [27] was administered to all participants to measure SCD severity, along with the SCD questionnaire. The ECog scale was developed to measure functional abnormalities in the elderly [28]. The ECog was scored on a Likert scale (1 = “better or no change” to 4 = “consistently much worse”) for each item and provides a global score and six domain scores (i.e., everyday memory, language, visuospatial abilities, planning, organization, and divided attention), ranging from 1 to 4, respectively.

Brain MRI and Amyloid PET

Brain MRI scanning was performed using a 3.0-Tesla scanner, including T1- and T2-weighted images, fluid-attenuated inversion

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recovery imaging, susceptibility-weighted imaging, and T1-weighted three-dimensional volumetric images. The severity of white matter hyperintensities (WMH) was evaluated using a visual rating scale by axial fluid-attenuated inversion recovery images and was rated as minimal (grade 1), moderate (grade 2), and severe (grade 3) [29]. The numbers of lacunes and cerebral microbleeds were counted as the previously described methods [30, 31]. Medial temporal lobe atrophy (MTA) was rated on a five-point scale (0–4 points) on T1-weighted coronal images [32]. MRI scans were evaluated by an experienced neurologist.

The participants underwent 18F-florbetaben PET, which was acquired in accordance with a standardized protocol [33]. Amyloid PET positivity was determined via a visual assessment in four brain areas (frontal cortex, lateral temporal cortex, posterior cingulate/precuneus, and parietal cortex) using a brain Aβ plaque load (BAPL) scoring system (1 = no BAPL, 2 = minor BAPL, 3 = significant BAPL; score 1 = negative, score 2 or 3 = positive) [34, 35] by a trained nuclear medicine specialist at each institution who was blinded to the clinical diagnosis. In addition, quantitative regional amyloid burden was measured using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8) and MATLAB 2014b (The MathWorks Inc., Natick, MA, USA) according to the previous methods [26]. The regional standardized uptake value ratio (SUVR) was obtained by calculating the median uptake over voxels in the regions of interest of PET images and dividing these values by those in the cerebellar cortex as the reference region. Global SUVR was calculated as the average of the 90 regional uptake values.

Statistical Analyses
Group differences (SCD only group vs. SCI) were assessed with two-sample t tests or Mann-Whitney U tests for continuous variables, and χ² or Fisher’s exact tests for categorical variables. Additional regression analyses between groups were performed to investigate the effects of demographic variables. Correlation analysis using Spearman’s correlation coefficients (ρ) was performed between SCD questionnaire and K-ECog scores across all participants. Comparisons of K-ECog cognitive domain-specific scores across all participants were performed using Friedman’s test with post hoc Wilcoxon signed-rank tests.

Statistical analyses were conducted using JMP Pro 11.0.0 (SAS Inc., Cary, NC, USA) and SPSS software package (version 19.0; SPSS Inc., Chicago, IL, USA). Significance was set at $p < 0.05$.

Results

Demographic Characteristics and Amyloid PET Results
Table 2 shows the clinical characteristics of the participants according to the absence or presence of SCI. There were no significant differences in age, sex, education, family history of dementia, and APOE ε4 carrier status between SCD individuals with and without SCI. With regard to cognitive measures, the SCI group had lower...
MMSE scores and showed lower performances in the RCFT copy, memory tests, and frontal/executive tests (Table 2). There were no differences in depressive symptoms, stress levels, severity of WMH, numbers of lacunes and microbleeds, and MTA between the two groups. For amyloid PET, SCD individuals with SCI had higher Aβ positivity ($p = 0.002$) and higher global SUVR values ($p = 0.048$) than the SCD only group. The results for Aβ positivity between the two groups remained significant after adjusting for age and education ($p = 0.014$).

**Self-Reported Questionnaire Scores**

The SCD questionnaire total scores were correlated with the K-ECog global (Spearman’s correlation coefficients $\rho = 0.474$, $p < 0.001$) and cognitive domain-specific scores ($\rho = 0.329–0.533$, $p < 0.001$). An overview of the group differences in the self-reported SCD questionnaire and the K-ECog scale is presented in Table 3. With regard to the SCD questionnaire, there were no differences in the SCD questionnaire total scores between the groups ($p = 0.733$). For SCD questionnaire items, most participants (97.50%) reported a decline in the memory domain as expected, and 54.17% of participants reported a cognitive decline in the nonmemory domain, while 42.50% of participants reported complaints in the language domain. The SCI group reported more complaints in the SCD visuospatial domain than the SCD only group (40.00% vs. 16.84%, $p = 0.012$), but there were no differences in com-

**Table 2.** Demographics and clinical characteristics of all SCD participants according to evidence of SCI

|                      | SCD total (n = 120) | SCD only (n = 95) | SCI* (n = 25) | $p$ value |
|----------------------|---------------------|-------------------|---------------|-----------|
| Age, year            | 70.87±6.10          | 70.41±5.95        | 72.60±6.49    | 0.111†    |
| Female               | 68 (56.67)          | 57 (60.00)        | 11 (44.00)    | 0.151     |
| Education, year      | 11.18±4.06          | 11.03±4.17        | 11.76±3.62    | 0.397     |
| Family history of dementia | 43 (35.83)    | 37 (38.95)        | 6 (24.00)     | 0.166     |
| APOE ε4 carriers     | 24 (20.00)          | 19 (20.00)        | 5 (20.00)     | >0.999    |
| K-MMSE               | 27.24±1.96          | 27.51±1.76        | 26.24±2.37    | 0.014     |
| Depressive symptoms: PHQ-9 | 2.94±3.71       | 3.04±3.69         | 2.56±3.81     | 0.183     |
| Stress levels: BEPSI-K | 1.54±0.78          | 1.55±0.78         | 1.52±0.77     | 0.836     |
| WMH, grade 1/2/3     | 85/30/5             | 70/21/4           | 15/9/1        | 0.326‡    |
| Lacunes, n (0/1/2)   | 108/10/2            | 84/10/1           | 24/0/1        | 0.133‡    |
| Microbleeds, n (0/1) | 109/11              | 84/11             | 25/0          | 0.117‡    |
| MTA, left (0–4 points) | 1.21±0.95         | 1.13±0.90         | 1.52±1.08     | 0.123     |
| MTA, right (0–4 points) | 1.12±0.86        | 1.05±0.82         | 1.40±0.96     | 0.123     |
| PET amyloid positivity | 26 (21.67)       | 15 (15.79)        | 11 (44.00)    | 0.002     |
| PET amyloid global SUVR | 1.27±0.24         | 1.23±0.19         | 1.41±0.34     | 0.048     |
| Neuropsychological tests§ |                  |                   |               |           |
| Forward digit span   | 0.60±1.10           | 0.66±1.06         | 0.36±1.27     | 0.193     |
| Boston naming test   | 0.39±1.03           | 0.46±1.03         | 0.13±0.97     | 0.218     |
| RCFT copy            | 0.24±0.62           | 0.31±0.56         | 0.05±0.76     | 0.038     |
| SVLT delayed recall  | 0.67±0.45           | −0.59±0.40        | −0.98±0.50    | 0.001     |
| RCFT delayed recall  | −0.04±0.78          | 0.08±0.79         | −0.46±0.63    | 0.002     |
| Digit symbol coding  | 0.46±1.03           | 0.67±0.97         | −0.33±0.86    | <0.001‡   |
| COWAT phonemic       | 0.18±1.03           | 0.31±1.05         | −0.31±0.80    | 0.007     |
| Trail making test-B  | 0.33±0.62           | 0.40±0.56         | 0.08±0.77     | 0.054     |
| Stroop test color reading | 0.13±0.82       | 0.27±0.74         | −0.42±0.88    | <0.001‡   |

Values are mean ± SD for continuous variables and numbers (%) for categorical variables. SCD, subjective cognitive decline; SCI, subtle cognitive impairment; APOE, apolipoprotein E; K-MMSE, Korean version of the Mini-Mental State Examination; PHQ-9, Patient Health Questionnaire-9; BEPSI-K, Korean version of the Brief Encounter Psychosocial Instrument; WMH, white matter hyperintensities; MTA, medial temporal lobe atrophy; SUVR, standardized uptake value ratio; RCFT, Rey Complex Figure Test; SVLT, Seoul Verbal Learning Test; COWAT, Controlled Oral Word Association Test. * SCI group, compared to the SCD only group, was defined as performance ≤ −1.0 SD on at least two neuropsychological tests. Mann-Whitney U (or †two-sample t) tests and χ² tests (or ‡ Fisher’s exact test) for comparisons between the SCD only group and SCD individuals with SCI were performed on continuous variables and categorical variables, respectively. § Each score is an age- and education-adjusted z-score.
plaints of other SCD cognitive domains between the groups. In addition, SCI group had less feeling of worse performance than peers than the SCD only group ($p = 0.017$), but there were no differences between the groups for the level of cognitive performance compared with peers ($p = 0.541$). For other SCD questionnaire items, there were no differences between the groups (Table 3).

Regarding the K-ECog scale, the average K-ECog global score of participants was $1.83 \pm 0.57$. Among cognitive domain-specific scores, the K-ECog memory scores ($2.22 \pm 0.74$) were higher than the other domain-specific K-ECog scores ($p < 0.001$), and the K-ECog language scores ($1.90 \pm 0.65$) were higher than the K-ECog visuospatial ($1.61 \pm 0.65$) and K-ECog executive scores ($1.67 \pm 0.59$) ($p < 0.001$). There were no differences in the K-ECog global scores and each domain-specific average K-ECog score (memory, language, visuospatial functioning, and executive functioning – planning, organization, and divided attention) between the two groups (Table 3).

**Discussion**

This study investigated the Aβ status by amyloid PET and self-reported cognitive decline status in SCD subjects with SCI compared to SCD only subjects within the CoS-
Co project. Subtle but detectable cognitive impairment that does not fulfill MCI criteria may exist as the first symptomatic phenomenon in the clinical spectrum of AD [3]. SCD could be the self-awareness of these subtle cognitive changes, but individuals with SCD may or may not present the subtle cognitive changes that represent the transitional phase preceding MCI. Therefore, it is important to investigate the clinical relevance of SCD and/or subtle cognitive changes in elderly individuals with medical help-seeking for subjective cognitive complaints.

Regarding the amyloid pathology in SCD, the present study investigated the Aβ status of SCD depending on the presence of SCI. Few studies have investigated subtle cognitive decline and Aβ status. One study showed that subtle executive deficits are related to higher brain Aβ deposition and lower grey matter volume in SCD [15]. Another study showed objective subtle cognitive difficulties were associated with faster amyloid deposition and early neurodegenerative changes relative to cognitively normal participants [8]. These results are consistent with the current results, which show more Aβ positivity in SCI participants with SCI. However, the previous studies have focused on the concept of subtle cognitive decline without mentioning the SCD status of the participants.

Self-reported cognitive decline is necessary for SCD classification. Regarding the severity of self-reported cognitive decline, few studies have investigated the clinical relevance of the severity of self-reported cognitive decline in SCD [36, 37]. In the current study focusing on subtle cognitive deficits, there were no differences in the severity of self-reported cognitive decline between SCD individuals with and without SCI. These results might suggest the limited role of self-reported cognitive decline in detecting subtle cognitive changes in elderly people with subjective cognitive complaints. However, due to the small sample size, our findings need to be replicated in further studies. In addition, 21% of total SCD participants were classified as SCI in the present study, comparable with other studies (22–23%) [10, 38]. However, due to relatively small number of SCI group, these findings also need to be replicated in larger samples. In the large sample study of the Alzheimer’s Disease Neuroimaging Initiative, 21% of cognitively normal participants had SCI irrespective of SCD [5]. Another issue in regard to SCD is that it may relate to psychiatric symptoms (e.g., depression, anxiety) and certain personality traits (e.g., neuroticism) [1, 39, 40]. Therefore, these affective factors and personality traits can be considered as the potential variables that can affect SCD on the studies.

To measure the severity of self-reported cognitive decline, we used two self-reported questionnaires. There were no differences in the severity of self-reported cognitive decline measured by the SCD questionnaire total scores and the K-ECog scores between SCD individuals with and without SCI. For SCD questionnaire items, the SCD only group had a greater feeling of worse performance than peers than the SCI group, but there were no differences in scoring on a Likert scale (range 1–5) for the level of cognitive performance compared with peers (Table 3). However, due to the small sample size, it is inconclusive whether “less feeling of worse performance than others” in the SCI group could suggest reduced self-awareness of SCD individuals with subtle cognitive deficits. In addition, the SCD Initiative Working Group proposed the inclusion of questions on subjective change in other cognitive domains, along with subjective memory decline in studies on SCD [1]. For the types of SCD cognitive complaints in the current study, the most common SCD was complaints in memory domain, followed by complaints in the language domain. Furthermore, the SCI group had more complaints of SCI visuospatial function than the SCD only group. Further studies are needed to determine whether there might be differences in the types of cognitive complaints in the nonmemory cognitive domain between SCD individuals with and without SCI.

Stage 3 of the NIA-AA preclinical AD criteria includes subtle cognitive decline, but there is no guidance on how this should be operationalized. Recent studies have defined subtle cognitive decline using cognitive composite measures of memory [41, 42] or global neuropsychological scores [43, 44], individual neuropsychological test scores by a score more than 1 SD below the normative mean on two of the six neuropsychological tests used in different cognitive domains [21], or sensitive memory process scores [11]. The subtle cognitive decline operationalization used in the current study used individual neuropsychological tests, an approach based on methods [11, 21] derived from the well-validated Jak/Bondi criteria for MCI [45], which balances reliability (reducing the possibility disproportionally impacted by only one poorly performed test in methods using a composite score) and sensitivity. Regarding MCI classification, some studies showed that conventional criteria for diagnosing MCI may be susceptible to false-positive cases [45–47]. Therefore, they suggested that using an actuarial neuropsychological method for MCI may yield AD biomarker association, more stable diagnoses, and prediction of progression than using a conventional diagnostic method [45].
There are some limitations to our study. This was the cross-sectional study limited to SCD individuals. Controls without both SCD and SCI were not included in this study. Therefore, we could not determine whether SCI reflects future cognitive decline, and there are some restrictions for evaluating the clinical relevance of SCD only group compared with controls. Our ongoing longitudinal CoSCo study which extends participants into control group will help verify these results and find out the long-term clinical significance of SCI. In addition, this was a relatively small sample of participants recruited from memory clinics. Therefore, the application of these results to a general population is limited. It is known that recruitment methods (population-based, community volunteer, or clinic-based samples) affect demographic (age, education, family history of dementia) and neuropsychological characteristics of the SCD participants among studies [48, 49]. In addition, clinic-based samples have more progression risk and AD-like feature than other samples although there are conflicting findings [50–52]. The study setting should be considered when evaluating SCD. Therefore, our results should be confirmed in larger samples, including those from the community. Furthermore, the assessment of functional limitations in everyday life is important when assessing cognitive functions. In this study, the ECog scale can assess functional abilities that are linked to specific cognitive abilities, because it was developed to capture relatively mild functional changes in measuring everyday function in older adults [28, 53]. However, evaluating instrumental activities of daily living in detail would be helpful for a functional assessment in SCD.

In conclusion, the present study, which investigated Aβ and self-reported cognitive decline status in SCD subjects, demonstrated that SCI is associated with Aβ positivity, but is not associated with the severity of self-reported cognitive decline, compared to SCD only subjects. These results suggest that the recognition of objectively defined subtle cognitive deficits may contribute to the early detection of AD in individuals with SCD. Therefore, elderly people with both SCD and subtle cognitive changes need to be further characterized using biomarkers, since they may represent the first detectable cognitive impairment in the clinical spectrum of AD.

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Statement of Ethics

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 (INHAUH2018-08-006-005). All participants provided informed consent, and the study was conducted in accordance with the Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S.Y.R. and D.W.Y. contributed to the design and concept of the study, S.H., J.H.J., K.H.P., M.J.W., S.H.C., and D.W.Y. contributed to the acquisition of data. S.H. evaluated MRI scans. S.Y.R. analyzed the data, performed interpretation of data, and wrote the first draft of the paper. D.W.Y. obtained funding and supervised the study. S.Y.R., Y.J.H., S.H., J.H.J., K.H.P., S.K., M.J.W., S.H.C., and D.W.Y. contributed to revising the manuscript for content and approved the final version.

Data Availability Statement

The data that support the findings of this study are openly available in (Open Science Framework) at https://osf.io/z6dc3/.
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