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Comprehensive Clinical and Behavioral Characteristics of Mild Cognitive Impairment According to Amyloid Positivity: A Large Multi-Center Korean Cohort

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ABSTRACT

Background and Purpose: Mild cognitive impairment (MCI) is a transitional stage to dementia, Alzheimer's disease being a major cause. Although amyloid beta-positive (Aβ+) MCI has been well-characterized, Aβ-negative (Aβ−) MCI has not. This study compared the comprehensive clinical and behavioral characteristics of Aβ+ and Aβ− MCI in a large multi-center cohort to better understand the heterogeneity of MCI, and to identify contributing factors to cognitive impairment.
Methods: A total of 686 MCI participants were included. Aβ positivity was determined using Aβ positron emission tomography imaging with a direct conversion Centiloid cutoff value of 25.5. Standardized assessment and questionnaires were used to collect a wide range of clinical information, including vascular risk factors, cognition, daily living function, neuropsychiatric symptoms, and lifestyle behavior. Groups were compared using independent *t*-tests and χ^2 tests.
Results: Aβ+ participants (n=406) were older, predominantly female, and more likely to be ApoE4 carriers. In contrast, Aβ− participants (n=280) showed higher vascular risk factors, including diabetes, elevated body mass index, and higher C-reactive protein levels. Aβ+ participants exhibited worse global cognition and functional decline, with a higher prevalence of delusions and appetite disturbances. Meanwhile, Aβ− participants reported greater social engagement, but poorer sleep quality.
Conclusions: This study highlights the distinct clinical and lifestyle profiles of Aβ+ and Aβ− MCI, illuminating the heterogeneity of MCI and its underlying factors in the Korean population.

Keywords: Mild Cognitive Impairment; Amyloid; Alzheimer Disease; Cognitive Decline

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Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

Conceptualization: Kim SA, Kim Y, Na DL, Seo SW, Jang H; Data curation: Kim SA, Kim Y, Na DL, Seo SW, Jang H; Formal analysis: Kim SA, Jang H; Funding acquisition: Na DL, Seo SW, Jang H; Investigation: Kim SA, Kim Y, Na DL, Seo SW, Jang H; Methodology: Kim SA, Kim Y, Jang H; Project administration: Na DL, Seo SW, Jang H; Resources: Kim Y, Na DL, Seo SW, Jang H; Supervision: Na DL, Jang H; Validation: Kim SA; Visualization: Kim SA; Writing - original draft: Kim SA; Writing - review & editing: Kim SA, Jang H.

INTRODUCTION

Mild cognitive impairment (MCI), increasingly prevalent with aging, is a heterogeneous condition that represents an intermediary stage between normal aging and dementia.[1,2] Alzheimer's disease (AD), a major cause of MCI, accelerates cognitive decline and worsens clinical outcomes.[3] AD is characterized by the pathologic accumulation of amyloid beta (Aβ) plaques. Aβ positron emission tomography (PET) identifies MCI caused by AD, and serves as a prognostic marker for dementia conversion.[4-6] Thus, many previous studies have focused on the clinical characteristics of and predictive factors for Aβ-positive (Aβ+) MCI.[7-10]

Few studies have thoroughly examined how clinical characteristics, including behavioral patterns, differ between Aβ+ and Aβ–negative (Aβ−) MCI participants in South Korea. Individuals with Aβ− MCI frequently visit memory clinics due to significant cognitive complaints. While specific clinical factors likely contribute to their cognitive impairment, these factors have often been overlooked in research. This oversight highlights the need for a comprehensive investigation into the clinical characteristics of Aβ− MCI to better comprehend its underlying causes. To achieve this, comparisons between Aβ+ and Aβ− MCI populations would provide valuable insights. Expanding this knowledge may facilitate targeted interventions to improve outcomes in both Aβ+ and Aβ− MCI.

Therefore, this study aimed to compare the comprehensive clinical characteristics of Aβ+ and Aβ− MCI participants, including cognitive and functional abilities, neuropsychiatric symptoms, and lifestyle behavior. A large multi-center MCI cohort in South Korea, characterized by well-standardized diagnostic processes and detailed questionnaires, was used. We hypothesized that Aβ+ MCI (MCI due to AD) would exhibit worse cognition, whereas in Aβ− MCI participants, other factors known to affect cognition, such as vascular risk factors or depression, might be more prominent. This study aims to contribute to deeper understanding of the heterogeneity of MCI and its underlying causes in the Korean population.

METHODS

Study participants

Between May 2019 and May 2022, 1,700 participants were enrolled in the Precision Medicine Platform for MCI based on multi-omics, imaging, evidence-based R&BD (PREMIER) consortium, a large-scale, multi-center study involving 25 centers across South Korea. The consortium aimed to establish a research platform for early diagnosis and precision medicine approaches in MCI, focusing on Alzheimer's clinical syndrome. The study included cognitively unimpaired (CU)[11] individuals and dementia of the Alzheimer's type (DAT)[12] as normal and active control groups, respectively.[11-13] Additionally, individuals with frontotemporal dementia[14,15] were included as an active control group, without classification based on cognitive stage.

For this study, MCI participants were selected exclusively from the Alzheimer's clinical syndrome. Among 1,700 participants, 57 participants diagnosed with frontotemporal dementia and 869 participants diagnosed with CU or DAT (defined by clinical judgment or Korean Instrumental Activities of Daily Living [K-IADL] ≥0.4) were excluded. In addition, 81 participants with incomplete Aβ data (e.g., missing amyloid PET or magnetic resonance

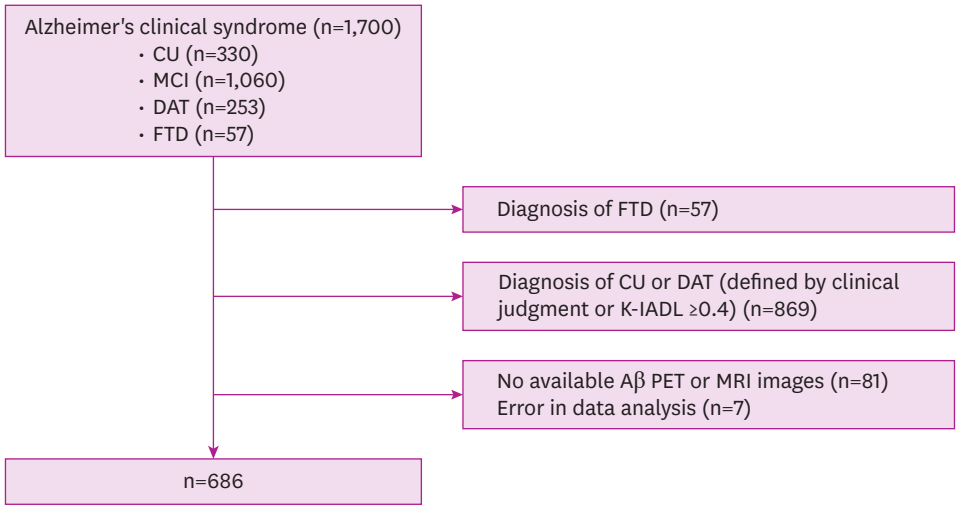

Fig. 1. Flowchart of the study. Flowchart depicting the inclusion and exclusion of participants from the study. A total of 1,700 individuals were initially assessed; after excluding participants other than FTD, CU, DAT (defined by clinical judgment or K-IADL ≥0.4) and missing images or errors in data analysis, 686 participants were included in the final analysis.
CU: cognitive unimpaired, MCI: mild cognitive impairment, DAT: dementia of the Alzheimer's type, FTD: frontotemporal dementia, K-IADL: Korean Instrumental Activities of Daily Living, Aβ: amyloid beta, PET: positron emission tomography, MRI: magnetic resonance imaging.

imaging [MRI]), and 7 participants with data analysis errors, were excluded. The final sample thus included 686 MCI participants (**Fig. 1**).[12]

Participants visiting memory clinics were recruited for this nationally funded study without selection bias. The study included a range of evaluations, including detailed questionnaires, neuropsychological assessments, ApoE genotyping, Brain MRI, and Aβ PET imaging. Individuals who had a psychiatric diagnosis, active cancer, unstable medical conditions, or a history of neurosurgery were excluded. Those with severe white matter hyperintensities, indicative of subcortical vascular cognitive impairment, were excluded from the outset, due to the primary focus of the study on AD-related cognitive impairment.

The study was approved by the Institutional Review Board of each participating center (SMC 2020-01-024-022), and conducted in accordance with the ethical principles of the Declaration of Helsinki. All participants provided written informed consent.

Aβ PET imaging acquisition, quantification, and cutoff for Aβ positivity

Aβ uptake was measured employing standardized PET imaging protocols with either 18F-florbetaben (FBB) or 18F-flutemetamol (FMM). PET scans were acquired 90 minutes after injection, and established algorithms used to reconstruct images.[16] Global Aβ uptake on FBB and FMM PET was measured using MRI-based direct conversion Centiloid (dcCL) values, following the image processing methodology described in a previously published study.[16] Aβ positivity was determined using a global dcCL cutoff value of 25.5.

Sensory function assessment

Sensory function was assessed employing self-reported questionnaires. Visual impairment was categorized as normal or impaired, impairment being defined as difficulties in daily functioning despite wearing glasses. Hearing difficulty was classified into 3 categories:

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normal; mild hearing loss (requiring hearing aids for daily functioning with adequate improvement); and severe hearing loss (where significant difficulties persisted, even with hearing aids).

Vascular risk factors and laboratory findings

Data were collected through self-reported and caregiver-reported questionnaires. Fasting blood samples included measurements of glycated hemoglobin (HbA1c), fasting plasma glucose, insulin, C-reactive protein, total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and estimated glomerular filtration rate (eGFR). Vascular risk factors were evaluated by means of a history of diagnosis or current medication use, and supplemented by fasting blood sample measurements. Hypertension and dyslipidemia were defined as a history of diagnosis or ongoing treatment. Diabetes mellitus was defined based on a reported diagnosis, current use of antidiabetic medication, or a HbA1c level exceeding 6.5%.[1] The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation, incorporating age, sex, and serum creatinine levels.[17] Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Alcohol consumption and smoking were assessed by means of a questionnaire, and categorized as binary variables (Yes/No), based on self-reported status.

Assessment of cognition

Cognition was assessed by the Mini-Mental State Examination (MMSE),[18] and the Clinical Dementia Rating-Sum of Boxes (CDR-SOB),[19] administered by trained neuropsychologists. Participants completed the Seoul Neuropsychological Screening Battery, which includes detailed tests of cognitive domains, such as attention, language, visuospatial ability, memory, and executive function.[19,20] These assessments were further adjusted for age, sex, and years of education.

Questionnaires on functional, neuropsychiatric, and behavioral characteristics

The Korean-Everyday Cognition (K-ECog), a 39-item caregiver-reported questionnaire, assessed everyday cognitive functions that included memory, language, visuospatial abilities, and executive functions, using a 4-point scale to compare current abilities to those from 10 years earlier.[21,22] The K-IADL evaluated instrumental daily activities using 11 items scored on a 4-point scale (0–3), with averages (= Sum of Points for 11 Items/11) calculated.[23] Neuropsychiatric symptoms were assessed using the Korean version of the Neuropsychiatric Inventory,[24,25] which evaluated 12 domains over the preceding 4 weeks. Frequency (0–4) and severity (0–3) were multiplied for each domain, and the total score was calculated as their sum, ranging (0 to 144). Total scores and the presence of each symptom (prevalence) were evaluated.

Participant-reported questionnaires included the (0–15) short form Geriatric Depression Scale,[26,27] and the (0–20) Geriatric Anxiety Inventory,[28,29] both of which used dichotomous response scales. Additionally, the Geriatric Quality of Life–Dementia Scale,[30] a 15-item questionnaire, assessed quality of life, with a total score ranging (15–60).

Lifestyle and behavioral patterns were primarily reported by caregivers. Involvement in cognitive and social activities was assessed by means of a 17-item questionnaire that evaluated the duration of each activity (i.e., the time spent on each occurrence of the activity), and the frequency of the activity over the past year (i.e., how often it was performed). Frequency was categorized as “not at all,” “less than once a month,” “once a

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month," "twice a month," "once a week," and "daily." These categories were converted into numerical values representing the estimated number of occurrences per month (e.g., 0, 0.5, 1, 2, 4, 30). The monthly frequency was then multiplied by the duration (in hours) to calculate the total time spent on the activity per month. The assessed 17 activities included the following: 'Television' describes watching television programs, while 'radio' describes listening to radio broadcasts. 'Reading' includes books, newspapers, or magazines, and 'learning' encompasses activities like using a computer, learning a foreign language, or playing a musical instrument. 'Creativity' describes engaging in writing, drawing, painting, or taking photographs. 'Internet' use includes searching for information, managing a personal homepage, blogging, and other online activities. 'Driving' describes operating a personal vehicle, while 'communication' comprises making phone calls, sending text messages, or exchanging messages with others. 'Socializing' includes attending gatherings, such as meetings, school reunions, or other social events. 'Caregiving' describes providing care or support to family members. 'Religion' includes engaging in prayer, meditation, worship services, or attending religious gatherings. 'Volunteering' involves participating in volunteer work, or helping neighbors. 'Housekeeping' includes engaging in household activities, such as cleaning, organizing, or fixing household items. 'Gaming' involves playing board games, such as chess, card games, or computer games. 'Exercise' describes engaging in physical activities, such as walking, hiking, or playing sports. 'Travel' refers to sightseeing, making excursions, shopping, or driving trips. 'Culture' describes attending movies, performances, exhibitions, museums, or sports events.

Physical activity was measured using the International Physical Activity Questionnaire (IPAQ),[31] which recorded the duration and frequency of vigorous and moderate activities, walking, and sedentary behaviors over the past 7 days. These data were converted into Metabolic Equivalent Task (MET) minutes per week by multiplying the time spent on each activity by its frequency and the corresponding MET values of 3.3 for walking, 4 for moderate activity, and 8 for vigorous activity.[31]

Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI),[32] a self-reported questionnaire that evaluates sleep patterns over the past month. The PSQI includes 7 components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. Each component is scored on a scale ranging (0 to 3), resulting in a total score ranging (0 to 21). Total scores above 5 indicate poor sleep quality.

Dietary patterns were evaluated using the Mini Dietary Assessment Index,[33] a 10-item questionnaire designed to measure nutrition and overall dietary quality. The items included recommended food elements (e.g., milk, meat, vegetables, fruits), limited food elements (e.g., high-fat, salty, or sugary foods), and dietary lifestyle factors (e.g., variety and regulation). Each item was rated on a 3-point scale (1, 3, 5), resulting in total scores ranging (10 to 50), where higher scores indicated healthier dietary patterns.

Statistical analysis

Independent-sample *t*-tests were used for continuous variables, and χ^2 tests were applied to categorical variables to compare the clinical characteristics between the 2 groups. The significance level was set at $p<0.05$. All analyses were performed with R software version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org).

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RESULTS

Demographics and clinical characteristics

Table 1 summarizes the demographic and clinical characteristics of MCI participants, comprising 686 individuals, of whom 280 (40.8%) were Aβ+, and 406 (59.2%) were Aβ−. The Aβ+ group was older at 72.7±7.1 years versus 70.1±9.2 years (p<0.001), and included a higher proportion of females at 67.1% versus 59.4% (p=0.047), compared to the Aβ− group. Among vascular risk factors, the Aβ− group showed a higher prevalence of diabetes mellitus at 19.6% versus 26.8% (p=0.037), a higher BMI at 23.0±2.9 kg/m^2 versus 24.2±3.1 kg/m^2 (p<0.001), and a higher prevalence of alcohol consumption at 38% vs. 51.6% (p=0.001), compared to the Aβ+ group. In addition, Aβ− participants exhibited higher levels of C-reactive protein at 0.8±1.3 mg/L versus 1.4±3.3 mg/L (p=0.001), and HbA1c at 5.8%±0.7% versus 6.2%±3.1% (p=0.031) levels.

Cognitive, functional, and neuropsychiatric characteristics

First, we examined the prevalence of amnestic MCI, defined as cases where the z-score of either the verbal memory test (Seoul Verbal Learning Test Delayed Recall) or the visual memory test (Rey Complex Figure Test Delayed Recall) was ≤−1, within the Aβ+ and Aβ− groups. Among the Aβ+ group, 225 participants (80.4%) were classified as amnestic MCI, compared to among the Aβ− group at 272 participants (67.0%), which was significantly higher

Table 1. Demographic and clinical characteristics of mild cognitive impairment participants

Variables	Aβ+ (n=280)	Aβ− (n=406)	p-value
Age (yr)	72.7±7.1	70.1±9.2	<0.001
Sex (female)	188 (67.1)	241 (59.4)	0.047
Education (yr)	10.2±4.4	10.8±4.7	0.073
ApoE4 carrier	182 (65)	63 (15.5)	<0.001
Visual impairment*	7 (2.5)	22 (5.5)	0.098
Hearing difficulty†			0.128
Normal	254 (92.0)	355 (88.1)	0.126
Mild hearing loss	12 (4.3)	26 (6.5)	0.317
Severe hearing loss	7 (2.5)	8 (2.0)	0.830
Vascular risk factors			
Hypertension	140 (50)	207 (51)	0.860
Diabetes mellitus	55 (19.6)	109 (26.8)	0.037
Dyslipidemia	117 (42.4)	194 (48.1)	0.162
Stroke	7 (2.5)	20 (5)	0.165
Cardiac disease	20 (7.2)	42 (10.4)	0.202
Estimated glomerular filtration rate (mL/min/1.73 m^2)	87.0±15.2	87.4±16.1	0.726
Body mass index	23.0±2.9	24.2±3.1	<0.001
Smoking	60 (21.7)	115 (28.5)	0.057
Drinking	105 (38.0)	208 (51.6)	0.001
Laboratory findings			
Glycated hemoglobin (%)	5.8±0.7	6.2±3.1	0.031
Fasting plasma glucose (mg/dL)	105.1±28.4	105.7±24.4	0.745
Insulin (μU/mL)	6.9±9.3	6.0±6.5	0.178
C-reactive protein (mg/L)	0.8±1.3	1.4±3.3	0.001
Total cholesterol (mg/dL)	181.8±36.9	179.3±41.1	0.406
Triglycerides (mg/dL)	119.4±60.8	127.9±78.8	0.112
Low-density lipoprotein (mg/dL)	102.7±28.3	99.7±31.1	0.188
High-density lipoprotein (mg/dL)	56.8±13.2	56.4±13.0	0.737

Values are presented as the mean ± standard deviation or number (%), as appropriate. Sensory Function was assessed through self-reported questionnaires.
Aβ: amyloid beta.
*Defined as challenges in daily functioning, despite wearing glasses.
†Mild hearing loss: Hearing aids required for daily functioning, with adequate improvement when aids are used. Severe hearing loss: Persistent difficulties, even when using hearing aids.

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Table 2. Cognitive performance according to Aβ status in participants

Variables	Aβ+ MCI (n=280)	Aβ− MCI (n=406)	*p*-value
MMSE	24.3±3.7	25.8±3.5	<0.001
CDR-SOB	1.5±0.9	1.1±1.0	<0.001
Seoul Neuropsychological Screening Battery*			
Digit span forward	6.0±1.5	5.8±1.5	0.797
Digit span backward	3.7±1.3	3.5±1.1	0.486
Korean Boston naming test	44.8±10.2	42.3±9.1	0.298
RCFT copy score	30.3±6.3	28.6±7.6	0.034
SVLT recall	16.7±5.1	14.9±4.7	<0.001
SVLT delayed recall	4.1±3.0	2.3±2.5	<0.001
SVLT recognition	19.5±2.6	18.3±2.9	<0.001
RCFT recall	10.2±6.7	6.1±5.1	<0.001
RCFT delayed recall	9.9±6.5	5.5±5.2	<0.001
RCFT recognition	18.7±2.5	17.7±2.5	<0.001
COWAT animal	13.6±5.0	12.2±4.4	0.017
COWAT supermarket	14.9±6.4	13.3±5.5	0.017
COWAT phonemic	21.3±11.8	21.1±10.5	0.168
Stroop test color reading	74.9±28.4	65.1±29.5	0.006

Values are presented as the mean ± standard deviation, as appropriate.
Aβ: amyloid beta, MCI: mild cognitive impairment, MMSE: Mini-Mental State Examination, CDR-SOB: Clinical Dementia Rating-Sum of Boxes, RCFT: Rey Complex Figure Test, SVLT: Seoul Verbal Learning Test, COWAT: Controlled Oral Word Association Test.
*Adjusted for age, sex and education years.

(*p*<0.001). **Table 2** summarizes the cognition according to Aβ status in MCI participants. As expected, Aβ+ participants showed worse performance on MMSE at 24.3±3.7 versus 25.8±3.5 (*p*<0.001), CDR-SOB at 1.5±0.9 versus 1.1±1.0 (*p*<0.001), as well as all specific cognitive tests, except for the Digit-Span tests, Korean Boston naming test, and Controlled Oral Word Association Test phonemic.

Table 3 shows that when functional and neuropsychiatric characteristics based on the questionnaires were compared between the 2 groups, Aβ+ participants showed higher scores on K-ECog, compared to Aβ− participants (total score 1.8±0.6 vs. 1.6±0.5, *p*<0.001), indicating greater decline observed, specifically in daily life involving memory (2.3±0.8 vs. 1.9±0.7, *p*<0.001), visuospatial function (1.6±0.7 vs. 1.5±0.6, *p*=0.012), and executive functions manifested in planning, organizing, and sequencing. However, no significant difference was observed in daily life concerning language problems at 1.7±0.7 versus 1.6±0.7 (*p*=0.285). The K-IADL score indicated worse functional abilities in the Aβ+ group at 0.12±0.12 versus 0.08±0.11 (*p*<0.001). In caregiver-reported neuropsychiatric symptoms, although the total Neuropsychiatric Inventory scores did not differ between the groups, delusions at 7.9% versus 2.5% (*p*=0.002) and appetite/eating disorders at 25.8% versus 16.7% (*p*=0.005) were more frequent in the Aβ+ group. Other neuropsychiatric symptoms that included hallucinations, agitation, depression, anxiety, and sleep disturbances did not differ significantly between the groups; nor did quality of life, depression, or anxiety significantly differ between the 2 groups.

Lifestyles and behavioral characteristics

Table 4 summarizes the lifestyles and behavioral characteristics of MCI participants according to Aβ status. For cognitive and social activities, Aβ+ participants spent significantly less time (hour/month) on activities such as listening to the radio (5.5±20.5 vs. 15.6±44.7, *p*<0.001), using the internet (9.8±25.4 vs. 16.1±32.0, *p*=0.005), and driving (8.1±29.3 vs. 15.5±41.1, *p*=0.006). Time spent on traveling was also lower in the Aβ+ group at 3.8±11.1 versus 7.3±32.4 (*p*=0.041). Total time spent on cognitive and social activities was significantly less in the Aβ+ group, compared to the Aβ− group (233.9±143.6 vs. 257.7±164.1, *p*=0.045).

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Table 3. Functional and neuropsychiatric characteristics according to Aβ status in participants

Variables	Aβ+ MCI (n=280)	Aβ− MCI (n=406)	*p*-value
Korean-Everyday Cognition			
Memory	2.3±0.8	1.9±0.7	<0.001
Language	1.7±0.7	1.6±0.7	0.285
Visuospatial	1.6±0.7	1.5±0.6	0.012
Executive: Planning	1.6±0.7	1.4±0.6	0.001
Executive: Organizing	1.5±0.6	1.4±0.6	0.010
Executive: Sequencing	1.9±0.8	1.7±0.7	0.013
Total	1.8±0.6	1.6±0.5	<0.001
Korean Instrumental Activities of Daily Living	0.12±0.12	0.08±0.11	<0.001
Geriatric Quality of Life–Dementia Scale	36.6±8.4	35.3±9.0	0.065
Neuropsychiatric inventory			
Total score	1.7±2.2	1.4±1.8	0.114
Presence of symptoms			
Delusion	22 (7.9)	10 (2.5)	0.002
Hallucination	6 (2.2)	4 (1)	0.331
Agitation/Aggression	24 (8.6)	43 (10.6)	0.465
Depression/Dysphoria	77 (27.6)	113 (27.8)	1.000
Anxiety	49 (17.6)	57 (14)	0.252
Elation/Euphoria	4 (1.4)	9 (2.2)	0.575
Apathy/Indifference	46 (16.5)	61 (15)	0.681
Disinhibition	21 (7.5)	28 (6.9)	0.870
Irritability/Lability	67 (24)	90 (22.2)	0.637
Aberrant motor behavior	8 (2.9)	6 (1.5)	0.320
Sleep/Night-time behavior	57 (20.4)	75 (18.5)	0.590
Appetite/Eating disorder	72 (25.8)	68 (16.7)	0.005
Geriatric Depression Scale short form	4.2±3.9	3.7±3.7	0.097
Geriatric Anxiety Inventory	5.0±5.3	5.2±5.5	0.554

Values are presented as the mean ± standard deviation or number (%), as appropriate.
Aβ: amyloid beta, MCI: mild cognitive impairment.

Other activities, such as watching television, reading, learning, socializing, caregiving, and exercise, did not reveal statistically significant differences between the groups. Physical activity, assessed using the IPAQ, revealed no significant difference between the 2 groups. Sleep characteristics, measured using the PSQI, indicated that Aβ− participants had poorer sleep quality. The total PSQI score was higher at 5.0±3.6 versus 6.0±3.9 (p=0.001), and a greater proportion were classified as poor sleepers at 42.9% versus 56.2% (p=0.001) in the Aβ− group, compared to the Aβ+ group. Specific components, including subjective sleep quality at (1.0±0.8 vs. 1.2±0.8, p=0.002), sleep duration (0.7±1.0 vs. 0.8±1.0, p=0.019), sleep disturbances (1.1±0.5 vs. 1.2±0.6, p<0.001), and daytime dysfunction (0.5±0.7 vs. 0.7±0.8, p<0.001), were worse in the Aβ− group. Nutritional scores tended to be higher in Aβ+ participants at 38.2±5.5, compared to Aβ− participants at 37.3±6.0 (p=0.051), although there was no statistical significance.

DISCUSSION

In this study, we used a large multicenter cohort dataset to examine the differences between Aβ+ and Aβ− MCI participants in terms of a wide range of clinical, cognitive, and functional characteristics. Our major findings were that: (1) Aβ+ participants had more conventional AD risk factors, while Aβ− participants showed higher vascular risk factors; (2) while Aβ+ participants generally performed worse cognitively and functionally, there were no significant differences between the groups in tasks involving simple attention, phonemic generative naming, caregiver-observed daily language impairment, or psychological measures, such

Table 4. Behavioral characteristics of participants

Behavioral characteristics	Aβ+ MCI (n=280)	Aβ− MCI (n=406)	*p*-value
Cognitive/Social behavior			
Television	94.7±72.9	84.6±78.9	0.088
Radio	5.5±20.5	15.6±44.7	<0.001
Reading	10.4±18.4	11.0±21.4	0.679
Learning	4.24±23.7	3.3±19.1	0.576
Creativity	3.0±13.1	4.3±16.6	0.261
Internet	9.8±25.4	16.1±32.0	0.005
Driving	8.1±29.3	15.5±41.1	0.006
Communication	13.7±20.4	16.3±27.6	0.160
Socializing	5.4±17.7	5.9±19.0	0.702
Caregiving	26.8±84.0	24.5±75.8	0.713
Religion	3.4±11.1	4.5±12.5	0.218
Volunteering	0.8±4.7	1.0±5.5	0.634
Housekeeping	22.4±28.7	23.6±31.0	0.631
Gaming	4.2±14.7	5.2±18.8	0.418
Exercise	21.1±23.0	21.2±23.0	0.939
Travel	3.8±11.1	7.3±32.4	0.041
Culture	0.4±1.1	1.2±7.8	0.056
Total	233.9±143.6	257.7±164.1	0.045
International Physical Activity Questionnaire			
Total Metabolic Equivalent Task (minutes per week)	2,110.9±2,307.3	2,343.8±2,408.4	0.288
Pittsburgh Sleep Quality Index			
Poor sleeper (score ≥5)	120 (42.9)	228 (56.2)	0.001
Subjective sleep quality	1.0±0.8	1.2±0.8	0.002
Sleep latency	1.1±1.0	1.2±1.1	0.293
Sleep duration	0.7±1.0	0.8±1.0	0.019
Habitual sleep efficiency	0.5±0.9	0.5±0.9	0.605
Sleep disturbances	1.1±0.5	1.2±0.6	<0.001
Use of sleeping medication	0.3±0.8	0.4±0.9	0.232
Daytime dysfunction	0.5±0.7	0.7±0.9	<0.001
Total	5.0±3.6	6.0±3.9	0.001
Nutrition score	38.2±5.5	37.3±6.0	0.051

Values are presented as the mean ± standard deviation or number (%), as appropriate.
Aβ: amyloid beta, MCI: mild cognitive impairment.

as depression and anxiety; and (3) although Aβ− participants were more socially active, they reported poorer sleep quality.

Aβ+ participants showed typical AD risk factors that included old age, female, and ApoE4 carriers, which was consistent with previous knowledge.[34-36] However, Aβ− MCI participants, who experience cognitive impairment despite no AD pathology, also demonstrated distinct features. We found that Aβ− participants exhibited a higher prevalence of alcohol consumption, and vascular risk factors, including diabetes and higher BMI. These vascular risk factors, independent of Aβ pathology, may contribute to cognitive complaints through mechanisms such as reduced cerebral perfusion, endothelial dysfunction, or systemic inflammation.[37-41] Among various conventional vascular risk factors, diabetes warrants particular attention. Our findings regarding diabetes are consistent with a previous study that showed an inverse association with Aβ positivity.[42-45] While some studies reported a higher incidence of clinically diagnosed dementia in patients with diabetes,[46-48] autopsy studies have shown lesser Aβ pathology in patients with dementia and diabetes, compared to those without,[42-45] which suggest that neuronal damage beyond Aβ pathology may contribute to cognitive impairment in patients with diabetes. Another interesting finding was that the Aβ− group showed higher C-reactive protein levels than the Aβ+ group. This aligns with various studies that suggest that peripheral inflammation may play a distinct role in cognitive

impairment.[49-52] Our findings suggest that interventions for Aβ− participants should focus more on controlling vascular risk factors, including glycemic control, anti-inflammatory strategies, and lifestyle modifications; however, further research is needed to clarify the impact of these factors on cognition in the Aβ− population.[53-55]

As expected, Aβ+ participants showed overall worse cognitive and functional performance than Aβ− participants. However, in this study we focused on comparable performance between the Aβ+ and Aβ− groups. These 2 groups showed no significant difference in tasks involving simple-attention, Korean Boston naming test, and phonemic generative naming (e.g., Controlled Oral Word Association Test phonemic test) abilities. Possible explanations for this are that in the MCI stage, attention is not largely impaired. In addition, phonemic generative naming, rather than the semantic generative naming, may be more closely associated with frontal lobe function, which in the early stage of AD tends to be relatively preserved. We found that caregivers of Aβ− participants reported a similar level of impairment in language-related everyday cognition (as measured by the K-ECog), compared to caregivers of Aβ+ participants. This language-related impairment in daily living, as reported by caregivers, may reflect the common occurrence of word-finding difficulties in older adults, irrespective of Aβ positivity. In terms of neuropsychiatric symptoms, Aβ+ participants exhibited a higher prevalence of delusions and eating behavior change, these symptoms might serve as potential early indicators of Aβ-related neurodegeneration in the MCI stage. Depression, anxiety, and quality of life—anticipated contributors to cognitive decline—did not differ significantly between the groups. We hypothesized that depression is a major contributor to both subjective and objective cognitive impairment, even in the absence of Aβ pathology. However, the presence of these symptoms alone cannot reliably differentiate Aβ positivity.

While Aβ− participants showed higher levels of social and cognitive engagement, they reported poorer sleep quality. Specifically, they demonstrated greater involvement in cognitively and socially demanding activities, such as listening to the radio, driving, using the internet, and traveling, which require relatively higher levels of cognitive functioning.[56,57] In contrast to the expectation that the Aβ+ group might have poor sleep quality, considering that the glymphatic system facilitates Aβ clearance during sleep,[58,59] Aβ− participants exhibited poorer sleep quality that was characterized by shorter duration, increased disturbances, and greater daytime dysfunction. Thus, we consider that in the Aβ− group, sleep disturbances and subjective sleep problems may be one of the major contributors to cognitive impairment. In addition, Aβ− participants exhibited a tendency toward worse nutritional habits, suggesting that both sleep and nutrition may represent modifiable risk factors that require greater attention. Furthermore, distinctive characteristics observed in Aβ− participants, such as vascular risk factors, sleep disturbances, and nutritional habits, may interact with one another, as previous studies have suggested.[60,61] These interactions warrant further investigation to better understand their combined influence on cognitive impairment. However, the relatively higher nutrition scores in the Aβ+ group might reflect greater caregiver involvement, or structured dietary support. The reliance on self- and caregiver-reported data, and the potential for reverse causation bias, underscore the need for longitudinal studies with objective measures, to better understand how these factors interact and influence cognitive outcomes across Aβ status.

The notable strengths of this study include the use of a large, multi-center study of 686 MCI participants, aiming to enhance generalizability and minimize the biases associated

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with single-center studies. However, several limitations should be noted. First, although the cross-sectional design allows for the identification of associations, it does not establish causal relationships, emphasizing the need for further validation by means of longitudinal studies. Second, the reliance on self- or caregiver-reported questionnaires introduces risks of recall bias and measurement errors. Variability in caregiver familiarity with the daily routines and recall accuracy of the participant could also introduce potential biases or inaccuracies. Nevertheless, our study highlights the distinct clinical and lifestyle profiles of Aβ+ and Aβ− MCI, providing valuable insights into the heterogeneity of MCI and its underlying causes, which may inform tailored interventions according to Aβ positivity in the Korean population. Further research that incorporates biomarkers and neuropathological validation is necessary to elucidate the relative contributions, such as tauopathy, Lewy body disease, and other non-Aβ pathologies, to cognitive impairment in Aβ− MCI.

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