

Baseline Physical Frailty Predicts Clinical Outcomes During Lecanemab Therapy in Early Alzheimer's Disease: A Prospective Real-World Cohort Study

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Supplementary Methods

Diagnostic Criteria for Early AD and SCD

Early AD was defined as either mild cognitive impairment (MCI) due to AD or mild AD dementia. MCI was diagnosed based on Petersen's criteria, which require self- or informant-reported cognitive concerns, objective impairment on neuropsychological assessment, generally preserved activities of daily living, and no evidence of dementia [1]. For the diagnosis of early AD, all patients were required to meet the following criteria: (1) cognitive concerns reported by the patient or caregiver; (2) objective cognitive impairment in at least one cognitive domain, including memory, language, visuospatial function, or frontal/executive function, as assessed by a comprehensive neuropsychological battery; (3) clinical severity compatible with MCI or mild dementia, defined as a global Clinical Dementia Rating (CDR) score of 0.5 or 1; and (4) biomarker evidence of amyloid pathology confirmed by amyloid positron emission tomography (PET).

Subjective Cognitive Decline (SCD) was defined according to the Subjective Cognitive Decline Initiative (SCD-I) framework as persistent self-experienced cognitive decline despite normal performance on standardized neuropsychological testing [2, 3]. Individuals with SCD were required to have persistent subjective cognitive complaints without objective cognitive impairment on comprehensive neuropsychological evaluation, a global CDR score of 0.5, and amyloid positivity confirmed by amyloid PET.

Seoul Neuropsychological Screening Battery

All participants underwent neuropsychological evaluation using the Seoul Neuropsychological Screening Battery (SNSB). The SNSB comprehensively assesses major cognitive domains, including attention, language, visuospatial ability, memory, and frontal/executive function [4]. Attention was assessed with the forward and backward Digit Span Test [4]. Language function was evaluated using the Korean version of the Boston Naming Test [4]. Visuospatial ability was measured using the copy condition of the Rey–Osterrieth Complex Figure Test (RCFT) [4]. Memory was assessed using the Seoul Verbal Learning Test, together with the immediate recall, delayed recall, and recognition trials of the RCFT [4]. Frontal/executive function was evaluated using the Controlled Oral Word Association Test, the Korean Color–Word Stroop Test, and the Digit Symbol Coding Test [4]. The SNSB-D score was calculated by summing the weighted scores from five cognitive domains (attention, language, visuospatial function, memory, and frontal/executive function), yielding a total score ranging from 0 to 300 points, with higher scores indicating better global cognitive performance [5].

Plasma collection and p-tau217 assays

Plasma samples were collected at baseline, on the day of the first lecanemab infusion, before drug administration, and at 3 and 6 months after treatment initiation. Additional plasma samples were collected at 12 and 18 months when available. At each time point, peripheral venous blood was collected into EDTA tubes and processed according to the standard operating procedures of the National Biobank of Korea. Plasma was separated by centrifugation, aliquoted, and stored at -80°C until analysis.

Plasma p-tau217 concentrations were measured at a certified central laboratory (Bredis Healthcare Inc., Seoul, Republic of Korea) using the Simoa HD-X Analyzer (Quanterix, Billerica, MA, USA) and the ALZpath p-Tau217 Advantage PLUS Reagent Kit (Quanterix), according to the manufacturer's instructions. Plasma samples underwent a single freeze–thaw

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cycle before analysis. All assays were performed under standardized laboratory conditions with established quality control procedures.

APOE genotyping

APOE genotyping was performed at baseline using genomic DNA isolated from peripheral blood leukocytes. APOE ϵ 2, ϵ 3, and ϵ 4 alleles were determined by genotyping the two common APOE single-nucleotide polymorphisms, rs429358 and rs7412 [6]. Based on the allelic combinations of these variants, participants were categorized as APOE ϵ 4 non-carriers, ϵ 4 heterozygotes, or ϵ 4 homozygotes.

MRI acquisition

All MRI examinations were performed on a 3.0-T scanner (Philips 3.0T Ingenia Elition X; Philips Healthcare, Andover, MA, USA). The baseline MRI protocol comprised three-dimensional T1-weighted imaging (3D T1-weighted), three-dimensional fluid-attenuated inversion recovery (3D FLAIR), T2-weighted imaging, diffusion-weighted imaging (DWI), and susceptibility-weighted imaging (SWI).

3D T1-weighted images were acquired in the sagittal plane using an IR-TFE sequence (slice thickness 1.0 mm, no interslice gap, repetition time [TR] 8.28 ms, echo time [TE] 4.0 ms, flip angle 8°, matrix size 256 × 256). 3D FLAIR images were acquired in the sagittal plane (slice thickness 1.2 mm, reconstruction interval 0.6 mm, TR 4800 ms, TE 372 ms, inversion time 1650 ms, flip angle 90°, matrix size 288 × 287) and reconstructed into axial and coronal images for clinical evaluation. T2WI was acquired in the axial plane using a turbo spin-echo sequence (slice thickness 7.0 mm, TR 3000 ms, TE 80 ms, flip angle 90°, matrix size 500 × 375). DWI was acquired in the axial plane (slice thickness 5.0 mm, TR 3954 ms, TE 80 ms, flip angle 90°, matrix size 176 × 174). SWI was acquired in the axial plane (source slice thickness 1.0 mm, reconstruction interval 1.0 mm, TR 28 ms, flip angle 18°, matrix size 384 × 383).

Follow-up MRI examinations were performed using the same scanner and imaging protocol as those used at baseline. Baseline MRI scans were reviewed to determine treatment eligibility and safety, including assessment of white matter hyperintensities (WMH), the number of cerebral microhemorrhages, the presence of macrohemorrhage, cortical superficial siderosis (cSS), the number of lacunes, and the presence of territorial infarction.

Follow-up MRI scans were assessed for amyloid-related imaging abnormalities with edema or effusion (ARIA-E) and amyloid-related imaging abnormalities with hemorrhage (ARIA-H). ARIA-E was defined as vasogenic edema or sulcal effusion [7, 8], whereas ARIA-H was defined as new or worsening cerebral microhemorrhages, macrohemorrhage, or cortical superficial siderosis compared with baseline MRI [7, 8]. The severity of ARIA-E and ARIA-H was classified as mild, moderate, or severe according to established criteria [7-9]. ARIA-E severity was graded based on the extent and number of FLAIR hyperintense lesions [7-9]. Mild ARIA-E was defined as FLAIR hyperintensity confined to a single sulcal and/or cortical or subcortical white matter region measuring less than 5 cm [7-9]. Moderate ARIA-E was defined as a FLAIR hyperintense lesion measuring 5–10 cm in greatest dimension or involvement of more than one site, each measuring less than 10 cm [7-9]. Severe ARIA-E was defined as FLAIR hyperintensity greater than 10 cm accompanied by gyral swelling and sulcal effacement [7-9]. ARIA-H severity was graded according to the number of newly developed microhemorrhages or focal areas of superficial siderosis [7-9]. Mild ARIA-H was defined as four or fewer new microhemorrhages or one focal area of superficial siderosis [7-9]. Moderate ARIA-H was defined as five to nine new microhemorrhages or two focal areas of superficial

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siderosis [7-9], and severe ARIA-H was defined as ten or more new microhemorrhages or more than two areas of superficial siderosis [7-9].

All MRI scans were independently reviewed by two experienced readers, including a neuroradiologist and a neurologist, who were blinded to clinical information. Any discrepancies in interpretation were resolved by consensus.

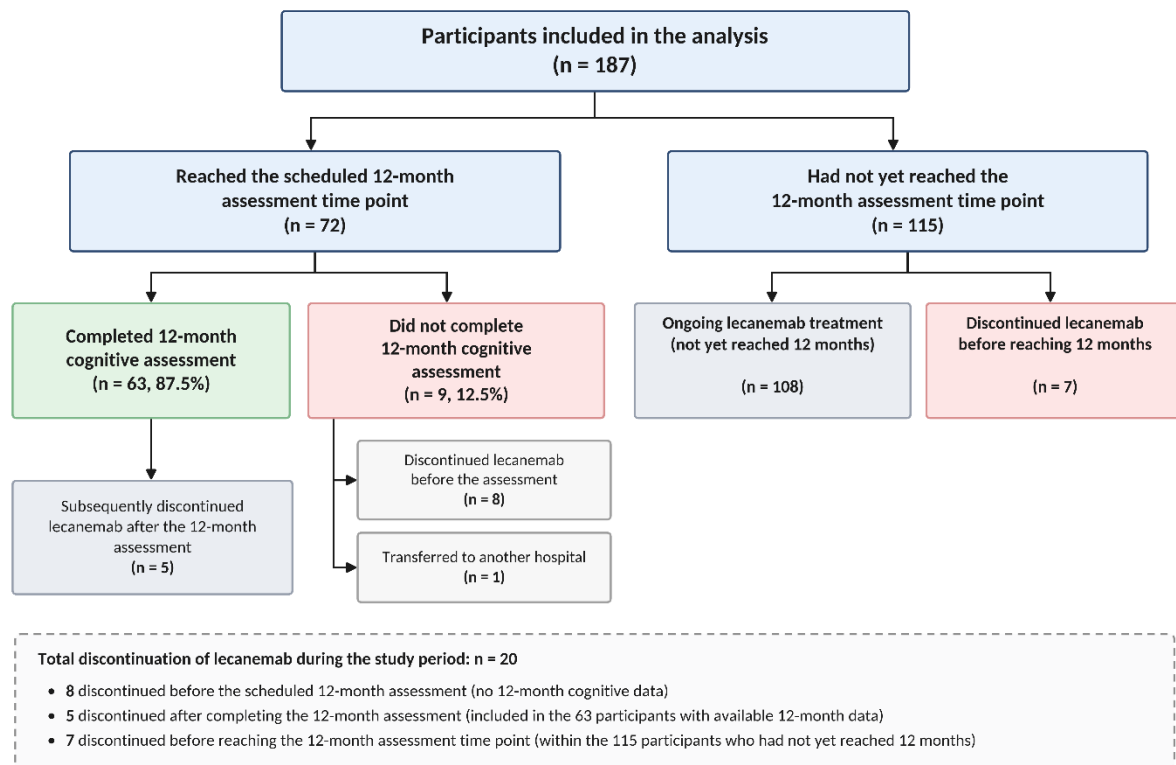
Amyloid PET acquisition and quantification

Amyloid PET imaging with 18F-florbetaben was performed before lecanemab initiation to determine treatment eligibility [9]. In most patients, PET images were acquired using a Discovery MI PET/computed tomography (CT) scanner (GE Healthcare, Waukesha, WI, USA). A 20-minute emission PET scan was obtained 90 minutes after the administration of a mean 18F-florbetaben dose of 296 MBq. Three-dimensional PET images were reconstructed using a 384×384 matrix with a voxel size of $0.65 \times 0.65 \times 2.79$. Reconstruction was performed with the ordered-subsets expectation maximization algorithm (iteration = 8 and subset = 34), incorporating time-of-flight and point-spread-function modeling.

All PET scans were independently interpreted by two experienced reviewers, including a nuclear medicine physician and a neurologist. Images were visually classified as amyloid-positive or amyloid-negative according to established appropriate use criteria [10, 11]. Any disagreements were resolved by consensus.

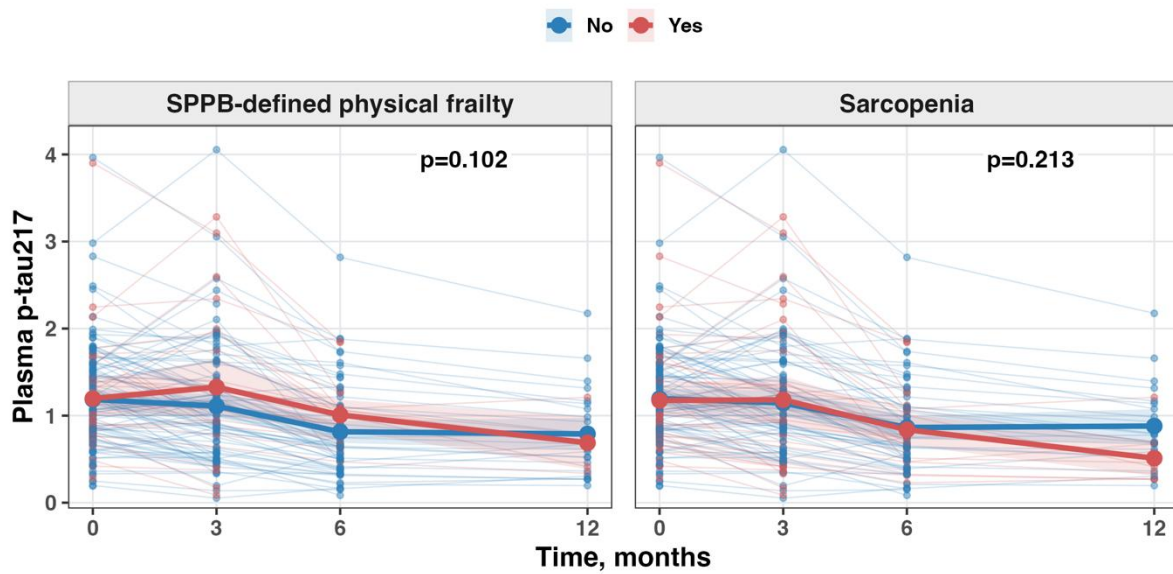
For quantitative analysis, all PET images were processed using the BTXBrain software platform (v1.1.2; Brightonix Imaging Inc., Seoul, Republic of Korea) to derive Centiloid (CL) values [12, 13]. The software provided automated quantitative values using PET images alone, without requiring accompanying CT or MRI data. Standardized uptake value ratio (SUVR) was calculated using the whole cerebellum as the reference region and subsequently converted to CL values.

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Supplementary Figure 1. Participant flow and availability of 12-month cognitive follow-up data. At the data cutoff, 72 of the 187 participants had reached the scheduled 12-month cognitive assessment time point, whereas 115 had not yet reached 12 months of follow-up. Among the 72 participants who had reached the 12-month assessment time point, 63 (87.5%) completed the scheduled cognitive evaluation; eight discontinued lecanemab before the assessment, and one was transferred to another hospital. Five of the 63 participants with available 12-month cognitive data subsequently discontinued lecanemab after completing the 12-month assessment. Among the 115 participants who had not yet reached the 12-month assessment time point, seven discontinued lecanemab before reaching this time point.

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Supplementary Figure 2. Plasma p-tau217 trajectory over time according to baseline physical vulnerability. Longitudinal trajectories of plasma p-tau217 levels are shown according to baseline SPPB-defined physical frailty and sarcopenia status. Points represent observed mean p-tau217 levels at each time point, and shaded bands indicate approximate 95% confidence intervals. Blue lines indicate participants without each condition, and red lines indicate participants with each condition. The p-values shown in each panel are for the time-by-group interaction from fully adjusted linear mixed-effects models adjusted for age, sex, years of education, APOE genotype, and baseline global CDR.

Plasma p-tau217 measurements were available for 153, 116, 83, and 31 participants at baseline, 3, 6, and 12 months, respectively.

Abbreviation: p-tau217, phosphorylated tau-217.

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Supplementary Table 1. Adjusted longitudinal associations of baseline physical frailty and sarcopenia with cognitive outcomes

Outcome	Exposure	β (95% CI), points/year	Nominal p	BH-FDR q
CDR-SB	SPPB-defined physical frailty	1.52 (0.98 to 2.05)	<0.001	<0.001
	Sarcopenia	1.40 (0.92 to 1.87)	<0.001	<0.001
MMSE	SPPB-defined physical frailty	−0.29 (−1.83 to 1.25)	0.708	0.708
	Sarcopenia	−0.90 (−2.26 to 0.46)	0.189	0.189
SNSB-D	SPPB-defined physical frailty	−11.36 (−22.38 to −0.34)	0.044	0.065
	Sarcopenia	−8.58 (−18.07 to 0.92)	0.076	0.114

Values are β coefficients (95% confidence intervals) for the time-by-exposure interaction and represent the estimated difference in the annual rate of change according to baseline exposure status.

Models were adjusted for age, sex, years of education, APOE $\epsilon 4$ genotype, and baseline global CDR. Benjamini–Hochberg correction was applied separately for each exposure across CDR-SB, MMSE, and SNSB-D, with the false discovery rate controlled at 5%.

Abbreviations: APOE, apolipoprotein E; BH-FDR, Benjamini–Hochberg false discovery rate; CDR-SB, Clinical Dementia Rating–Sum of Boxes; CI, confidence interval; MMSE, Mini-Mental State Examination; SNSB-D, Seoul Neuropsychological Screening Battery–Dementia version; SPPB, Short Physical Performance Battery

Supplementary Table 2. Sensitivity analyses of longitudinal cognitive outcomes after excluding participants with subjective cognitive decline

Outcome	Exposure	β (95% CI), points/year	Nominal p	BH-FDR q
CDR-SB	SPPB-defined physical frailty	1.47 (0.91 to 2.02)	<0.001	<0.001
	Sarcopenia	1.36 (0.85 to 1.87)	<0.001	<0.001
MMSE	SPPB-defined physical frailty	−0.31 (−1.95 to 1.33)	0.706	0.706
	Sarcopenia	−0.89 (−2.37 to 0.59)	0.234	0.234
SNSB-D	SPPB-defined physical frailty	−11.23 (−22.58 to 0.11)	0.052	0.078
	Sarcopenia	−6.19 (−16.47 to 4.09)	0.233	0.234

Analyses excluded 16 participants with subjective cognitive decline. The CDR-SB and MMSE models included 171 participants, and the SNSB-D models included 164 participants. Values are β coefficients (95% confidence intervals) for the time-by-exposure interaction and represent the estimated difference in the annual rate of change according to baseline exposure status.

Models were adjusted for age, sex, years of education, APOE $\epsilon 4$ genotype, and baseline global CDR. Benjamini–Hochberg correction was applied separately for each exposure across CDR-SB, MMSE, and SNSB-D, with the false discovery rate controlled at 5%.

Abbreviations: AD, Alzheimer disease; APOE, apolipoprotein E; BH-FDR, Benjamini–Hochberg false discovery rate; CDR-SB, Clinical Dementia Rating–Sum of Boxes; CI, confidence interval; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; SCD, subjective cognitive decline; SNSB-D, Seoul Neuropsychological Screening Battery–Dementia version; SPPB, Short Physical Performance Battery.

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