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ORIGINAL ARTICLE

Difference in trajectories according to early amyloid accumulation in cognitively unimpaired elderly

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Abstract

Background and purpose: Amyloid β (Aβ), a major biomarker of Alzheimer's disease, leads to tau accumulation, neurodegeneration and cognitive decline. Modelling the trajectory of Aβ accumulation in cognitively unimpaired (CU) individuals is crucial, as treatments targeting Aβ are anticipated. The evolution of Aβ levels was investigated to determine whether it could lead to classification into different groups by studying longitudinal Aβ changes in older CU individuals, and differences between the groups were compared.

Methods: A total of 297 CU participants were included from the Alzheimer's Disease Neuroimaging Initiative database, and these participants underwent apolipoprotein E (APOE) genotyping, neuropsychological testing, brain magnetic resonance imaging, and an average of 3.03 follow-up ^{18}F-florbetapir positron emission tomography scans. Distinct Aβ trajectory patterns were classified using latent class growth analysis, and longitudinal cognitive performances across these patterns were assessed with a linear mixed effects model.

Results: The optimal model consisted of three classes, with a high entropy value of 0.947. The classes were designated as follows: class 1, non-accumulation group ($n = 197$); class 2, late accumulation group ($n = 70$); and class 3, early accumulation group ($n = 30$). The late accumulation and early accumulation groups had more *APOE ε4* carriers than the non-accumulation group. The longitudinal analysis of cognitive performance revealed that the

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early accumulation group showed the steepest decline (modified Preclinical Alzheimer's Cognitive Composite with digit symbol substitution [mPACCdigit], $p<0.001$; modified Preclinical Alzheimer's Cognitive Composite with trails B [mPACCtrailsB], $p<0.001$) and the late accumulation group showed a steeper decline (mPACCdigit, $p=0.014$; mPACCtrailsB, $p=0.007$) compared to the non-accumulation group.

Conclusions: Our study showed the heterogeneity of Aβ accumulation trajectories in CU older individuals. The prognoses for cognitive decline differ according to the Aβ trajectory patterns.

KEYWORDS
Alzheimer's disease, amyloid, cognition, latent class growth analysis, longitudinal study, positron emission tomography, trajectory

INTRODUCTION

Amyloid β (Aβ) accumulation, considered a surrogate biomarker in Alzheimer's disease (AD), induces tau protein accumulation, eventually leading to neurodegeneration and cognitive decline [1, 2]. Preclinical AD is characterized by the presence of AD biomarkers in the absence of cognitive decline and is regarded as a crucial stage for the prevention of disease progression [3, 4]. Moreover, understanding the heterogeneous changes in Aβ accumulation amongst cognitively unimpaired (CU) older adults is important for effectively identifying individuals at risk and preventing cognitive decline.

In previous longitudinal studies aimed at investigating phenotypes and prognoses amongst CU older individuals, the conventional approach involved categorizing cases based on preselected variables, such as clinical disease stage or genotype [5–8]. However, this approach has limitations in classifying individuals with similar age-related change trajectories into multiple groups and comparing these trajectories effectively. The growth mixture modelling and latent class growth analysis (LCGA) techniques are valuable tools for identifying distinct temporal trajectories of change within a population [9]. Notably, few studies of trajectories are available that use growth mixture modelling or LCGA in CU older populations [10–12], and even fewer studies of Aβ accumulation trajectories.

Modelling the trajectory of Aβ accumulation amongst CU older individuals is crucial, given the expected advancements in Aβ-targeted treatments. It was hypothesized that the longitudinal course of Aβ accumulation in CU older adults would feature different patterns. Additionally, it was hypothesized that clinical progression and atrophic changes in the brain would vary according to the pattern of Aβ trajectories.

In this study, the aim was to categorize Aβ trajectories amongst CU older people into several groups using LCGA modelling. Furthermore, longitudinal differences in cognitive function and brain structure between the groups were examined.

METHODS

Clinical data collection

The data utilized in the present study were obtained from the ADNIMERGE dataset from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu), as of December 2019. ADNI, initiated in 2003 under the leadership of Michael W. Weiner, represents a collaborative effort of public–private partnership. The primary goal of ADNI is to investigate how serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical or neuropsychological assessments can be effectively integrated to measure the progression of mild cognitive impairment and early AD dementia. For the most recent information, please visit www.adni-info.org.

Study participants

Participants from ADNI-1 to ADNI-3 and ADNI GO were included in the present study if (i) baseline diagnosis was CU or subjective memory concern, and depending on the availability of (ii) valid ^{18}F-florbetapir (AV45) PET standardized uptake value ratios (SUVRs) that were followed up at least twice, (iii) longitudinal neuropsychological assessments and (iv) longitudinal assessment of hippocampal volumes (HVs). Baseline diagnoses were determined using standard criteria described in the ADNI procedure manuals (www.adni-info.org). Consequently, 297 participants met these criteria and were included in the present study.

The external validation sample involved 133 CU participants recruited from September 2015 to February 2024 at Samsung Medical Centre in South Korea.

All participants provided written informed consent and participated in protocols approved by the institutional review board of each participating site. Use and publication of the data were approved by the ADNI Data Sharing and Publications Committee.

For the external validation study, written informed consent was obtained from participants and their caregivers, and the institutional review board of Samsung Medical Centre approved the study protocol.

Neuroimaging data acquisition

Standardized uptake value ratios were obtained from UC Berkeley AV45 analysis data of the ADNI dataset (ida.loni.usc.edu). The target region of interest for AV45 PET SUVR is the cortical grey matter regions (including the frontal, anterior/posterior cingulate, lateral parietal and lateral temporal regions), and the reference region of interest is the whole cerebellum [13].

The current study used the HV neuroimaging data from the ADNIMERGE dataset. The detailed protocols for image acquisition are elaborated in a previous study [14] and at www.adni-info.org.

Neuropsychological assessment

All participants underwent longitudinal neuropsychological assessments using the ADNI-modified Preclinical Alzheimer's Cognitive Composite (mPACC) score, which was developed to detect early decline in the preclinical stages of the disease [15]. mPACCdigit includes (a) the Total Recall Score of the free and cued selective reminding test, (b) the Delayed Recall Score on the logical memory IIa (LM) subtest of the Wechsler Memory Scale, (c) the Digit Symbol Substitution Test score from the Wechsler Adult Intelligence Scale Revised and (d) the Mini-Mental State Examination (MMSE) total score. mPACCtrailsB includes (a) the Alzheimer's Disease Assessment Scale cognitive subscale Delayed Word Recall, (b) LM Delayed Recall, (c) MMSE total score and (d) Trail-Making Test B Time to Completion.

Statistical analyses

Latent class growth analysis was performed to detect potential distinct patterns in the trajectory of Aβ deposition in CU older individuals. The method has the advantage of allowing for the estimation of different parameters for each latent class because it considers the heterogeneity of the trajectory change present in the group [16, 17].

This study comprised three steps of data analysis. First, model fit statistics were compared to determine the number of latent classes and slope shape based on the following indices: Bayesian information criterion (BIC) [18]; sample size adjusted Bayesian information criterion (SSBIC) [19]; Lo–Mendell–Rubin adjusted likelihood ratio test (LMR-LRT) [20]; parametric bootstrapped likelihood ratio test (BLRT) [21]; and entropy. A lower BIC (or SSBIC) shows a better fit. As the entropy value approaches 1, classification becomes more accurate [22]. After determining the number and slope shape of the latent class, baseline characteristics of the latent classes were analysed using one-way ANOVA for continuous variables after evaluating normality with the Shapiro–Wilks test and chi-squared tests for categorical variables. Finally, to investigate longitudinal differences in neuropsychological outcomes and HVs between the latent classes, linear mixed effect modelling was performed using latent classes, time, age, sex, education level, detection of apolipoprotein E (*APOE*) *ε4*, intracranial volume (only for HV), and the interaction between trajectory group and time as fixed effects, whilst participants and time signalled random effects. *p* values were corrected using the Bonferroni method due to multiple testing.

Latent class growth analysis was conducted with Mplus version 8.3 [23]. All other analyses were performed using the R 4.2.1 package (Vienna, Austria; http://www.R-project.org/).

RESULTS

Demographic characteristics of participants

The baseline demographic characteristics of the study participants are presented in Table 1. The age of the participants was 73.8 ± 5.7 years (mean ± standard deviation). The proportion of *APOE ε4* carriers was 30.1%, and 52.5% were women. The median AV45 PET SUVR at baseline was 1.05, and median HV was 7491.5 mm^3. The average follow-up time for longitudinal AV45 PET SUVR, neuropsychological measurements and HV was 53.2 ± 24.2, 59.3 ± 23.6 and 31.8 ± 13.4 months, respectively.

Determining the number of latent classes

The BLRT was significant in all latent classes (Table 2). Entropy was very high, at values above 0.9 in all latent classes. The *p* value of

TABLE 1 Baseline demographic and neuropsychological characteristics of the study participants.

	Baseline CU participants (*N* = 297)
Age (years), mean (SD)	73.8 (5.7)
Female, *N* (%)	156 (52.5)
Education (years), mean (SD)	16.5 (2.7)
APOE ε4 carriers, *N* (%)	89 (30.1)
Baseline AV45 PET SUVR median [Q1, Q3]	1.05 [1.00, 1.16]
Baseline mPACCdigit mean (SD)	0.01 (2.93)
Baseline mPACCtrailsB mean (SD)	0.06 (2.67)
HV (mm^3), median [Q1, Q3]	7491.5 [6874.8, 7963.5]

Abbreviations: *APOE ε4*, apolipoprotein E; AV45, ^{18}F-florbetapir; CU, cognitively unimpaired; HV, hippocampal volume; mPACCdigit, modified Preclinical Alzheimer's Cognitive Composite with digit symbol substitution; mPACCtrailsB, modified Preclinical Alzheimer's Cognitive Composite with trails B; *N*, number; PET, positron emission tomography; Q, quantile; SD, standard deviation, SUVR, standardized uptake value ratio.

LMR-LRT was significant only in the class 2 model, whereas the class 3 model showed a *p* value close to the significance level. The difference of BIC (or SSBIC) points between a *k* − 1 and a *k* class model (*k* = 2, 3) indicated that two or more class models were a better fit. Additionally, the difference of BIC (or SSBIC) value between the model with three linear trajectories (linear/linear/linear, L/L/L) and the model with two linear and one quadratic trajectory (linear/quadratic/linear, L/Q/L) was small (<6). These results indicate that the goodness of fit between the L/L/L and L/Q/L models is similar. Therefore, the simpler model (L/L/L) was selected as the final model.

TABLE 2 Fit information for the latent class growth analysis of AV45 trajectories.

	Class 1, L	Class 2, L/L	Class 3, L/L/L	Class 3, L/Q/L
BLRT (*p* value)[a]		<0.001	<0.001	<0.001
Entropy		0.958	0.947	0.949
LMR-LRT (*p* value)[a]		0.004	0.091	0.076
△BIC[a]		723.82	307.60	310.77
△SSBIC[a]		733.32	317.12	323.46
BIC	−440.54	−1164.36	−1471.96	−1475.13
SSBIC	−523.00	−1256.32	−1573.44	−1579.78
Class 1 (*N* %)	297 (100.0)	236 (79.5)	197 (66.3)	199 (67.0)
Class 2 (*N* %)		61 (20.5)	70 (23.6)	69 (23.2)
Class 3 (*N* %)			30 (10.1)	29 (9.8)

Note: "△" represents the difference in BIC and SSBIC values between models.

Abbreviations: △, delta; AV45, ^{18}F-florbetapir; BIC, Bayesian information criterion; BLRT, parametric bootstrapped likelihood ratio test; L, linear; LMR-LRT, Lo–Mendell–Rubin adjusted likelihood ratio test; *N*, number; Q, quadratic; SSBIC, sample size adjusted Bayesian information criterion.

[a]Sequential comparison points between a model *k* − 1 and a model *k* (*k* = 2, 3).

Characteristics of latent classes in Aβ trajectory modelling

Figure 1 shows the AV45 PET SUVR trajectories for the class 3 model. Class 1, comprising an estimated 66.3% of the participants, indicated a group with low Aβ burden compared with baseline levels (intercept 1.015, standard error [SE] 0.009, $p < 0.001$; linear slope <0.001, SE = 0.001, $p = 0.644$; Table 3). Class 2, consisting of an estimated 23.6% of the participants, was characterized by an increase in Aβ levels over the same period from an initially low baseline level (intercept 1.095, SE = 0.022, $p < 0.001$; linear slope 0.013, SE = 0.002, $p < 0.001$). Class 3, which included an estimated 10.1% of the participants, had a baseline value of 1.388, which was greater than that of the other classes; this class consistently exhibited high Aβ levels compared with baseline values (intercept 1.388, SE = 0.059, $p < 0.001$; linear slope 0.012, SE = 0.004, $p = 0.002$). Thus, class 1 was designated as the 'non-accumulation group', class 2 with relatively late onset of amyloid accumulation as the 'late accumulation group' and class 3 with higher amyloid burden at baseline as the 'early accumulation group'.

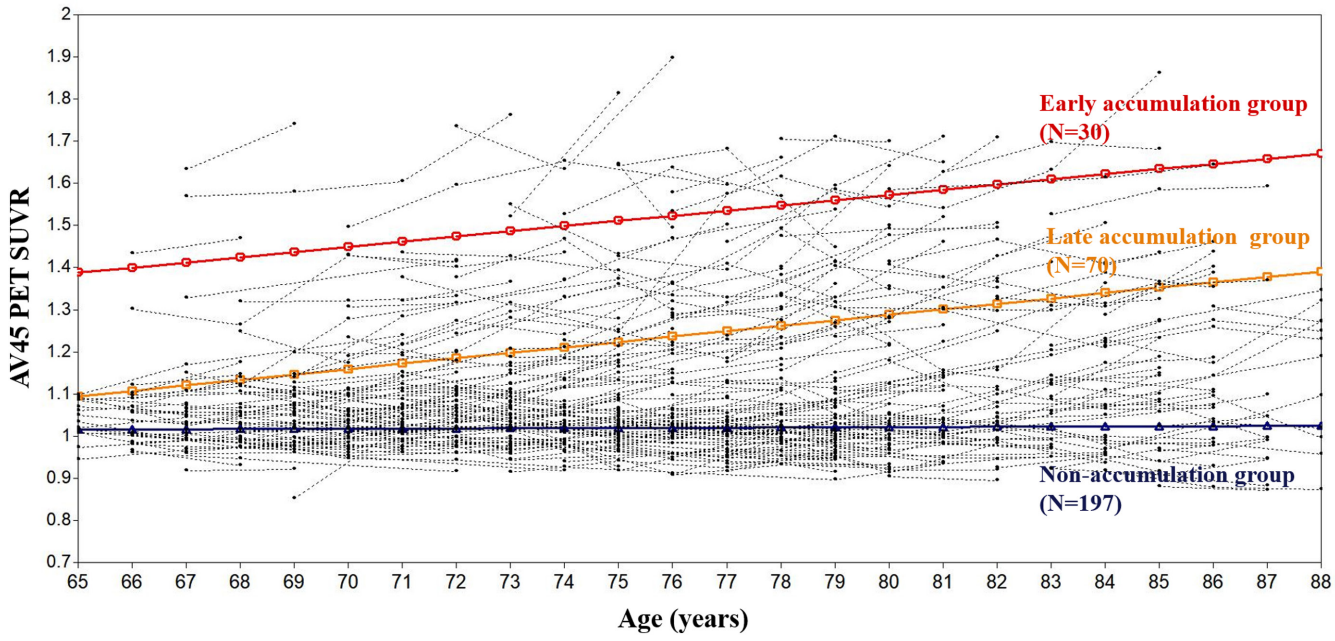

FIGURE 1 Trajectories of AV45 PET SUVRs for the class 3 model. Three groups were identified based on the trajectory of Aβ accumulation and designated as non-accumulation (dark blue), late accumulation (yellow) and early accumulation (red). Solid lines indicate the estimated trajectories for each group. Red, yellow and blue circles indicate estimated values at each age. On the vertical axis, late accumulation values represent a more severe condition. AV45, ^{18}F-florbetapir; SUVR, standardized uptake value ratio.

Baseline characteristics of the three Aβ trajectory groups

The baseline characteristics of the three Aβ trajectory groups based on the class 3 model are presented in Table 4. Carriers of the *APOE ε4* allele were most frequently present in the early accumulation group (70.0%), followed by the late accumulation group (40.0%) and the non-accumulation group (20.4%) (early accumulation vs. late accumulation group *p* value 0.018; early accumulation vs. non-accumulation group *p* value <0.001; late accumulation vs. non-accumulation group *p* value 0.004). No significant differences were found regarding age, sex or education level amongst the three groups. Moreover, no differences were recorded in the mPACC scores and mean HV amongst the three groups at baseline.

Longitudinal changes in the three Aβ trajectory groups

The longitudinal changes in the outcomes of the neuropsychological tests amongst the three Aβ trajectory groups are presented in Table 5 and Figure 2. The late accumulation and early accumulation groups revealed steeper slopes in mPACCdigit and mPACCtrailsB scores than the non-accumulation group (late accumulation group, β coefficient [*B*] = −0.027, corrected $p = 0.014$ for mPACCdigit and $B = -0.024$, $p = 0.007$ for mPACCtrailsB; early accumulation group, $B = -0.071$, $p < 0.001$ for mPACCdigit and $B = -0.058$, $p < 0.001$ for mPACCtrailsB). Additionally, the early accumulation group exhibited a significantly faster decline than the late accumulation group in mPACCdigit and mPACCtrailsB scores ($B = -0.044$, $p = 0.007$ for mPACCdigit and $B = -0.035$, $p = 0.013$ for mPACCtrailsB).

Regarding HV, the linear mixed effect modelling analysis revealed a steeper decrease in the early accumulation group than in the non-accumulation group ($B = -5.759$, SE = 2.312, $p = 0.039$). However, the comparison between the late accumulation and the non-accumulation groups did not yield any significant difference in the longitudinal changes in HV ($B = -0.410$, SE = 1.753, $p = 0.815$). Similarly, no longitudinal differences in HV were noted between the early accumulation and late accumulation groups ($B = -5.349$, SE = 2.641, $p = 0.130$).

External validation

The baseline demographic characteristics of the validation sample are presented in Table S1. The mean age of the validation cohort was 71.1 years (age range 63–85 for the validation set and 65–88 for the

TABLE 3 Parameter estimates for trajectories of the class 3 model.

	Non-accumulation		Late accumulation		Early accumulation	
	B (SE)	*p* value	*B* (SE)	*p* value	*B* (SE)	*p* value
Intercept	1.015 (0.009)	<0.001	1.095 (0.022)	<0.001	1.388 (0.059)	<0.001
Linear	<0.001 (0.001)	0.644	0.013 (0.002)	<0.001	0.012 (0.004)	0.002

Abbreviations: *B*, β coefficient; SE, standard error.

TABLE 4 Clinical characteristics in three Aβ trajectory groups.

	Non-accumulation (*N* = 197)	Late accumulation (*N* = 70)	Early accumulation (*N* = 30)	*p* value[c]	*p* value[d]	*p* value[e]
Age (years), mean (SD)[a]	73.5 (5.8)	74.7 (6.0)	73.5 (4.6)	0.394	1.000	1.000
Female, *N* (%)[b]	94 (47.7)	43 (61.4)	19 (63.3)	0.146	0.333	1.000
Education (years), mean (SD)[a]	16.7 (2.6)	16.0 (3.0)	16.3 (2.5)	0.243	1.000	1.000
APOE ε4 carrier, *N* (%)[b]	40 (20.4)	28 (40.0)	21 (70.0)	0.004	<0.001	0.018
HV (mm^3), mean (SD)[a]	7506.8 (999.1)	7415.4 (972.9)	7255.0 (793.4)	1.000	0.666	1.000
mPACCdigit mean (SD)[a]	0.30 (2.78)	−0.53 (3.33)	−0.63 (2.68)	0.123	0.316	1.000
mPACCtrailsB mean (SD)[a]	0.35 (2.54)	−0.35 (2.94)	−0.86 (2.59)	0.165	0.059	1.000

Abbreviations: *APOE ε4*, apolipoprotein E; HV, hippocampal volume; mPACCdigit, modified Preclinical Alzheimer's Cognitive Composite with digit symbol substitution; mPACCtrailsB, modified Preclinical Alzheimer's Cognitive Composite with trails B; *N*, number; SD, standard deviation.

[a]One-way ANOVA (analysis of variance).

[b]Chi-square test.

Bonferroni corrections were performed for comparisons between.

[c]Non-accumulating and late accumulation.

[d]Non-accumulating and high-accumulating.

[e]Late accumulation and high-accumulating.

TABLE 5 Results of the linear mixed effect model for neuropsychological tests in three Aβ trajectory groups.

	Class × time					
	Late accumulation (ref. non-accumulation)		Early accumulation (ref. non-accumulation)		Early accumulation (ref. late accumulation)	
	B (SE)	*p* value	*B* (SE)	*p* value	*B* (SE)	*p* value
mPACCdigit	−0.027 (0.009)	0.014	−0.071 (0.013)	<0.001	−0.044 (0.014)	0.007
mPACCtrailsB	−0.024 (0.008)	0.007	−0.058 (0.011)	<0.001	−0.035 (0.012)	0.013

Note: *p* values were corrected using Bonferroni's method due to multiple testing.

Abbreviations: *B*, β coefficient; mPACCdigit, modified Preclinical Alzheimer's Cognitive Composite with digit symbol substitution; mPACCtrailsB, modified Preclinical Alzheimer's Cognitive Composite with trails B; ref, reference group; SE, standard error.

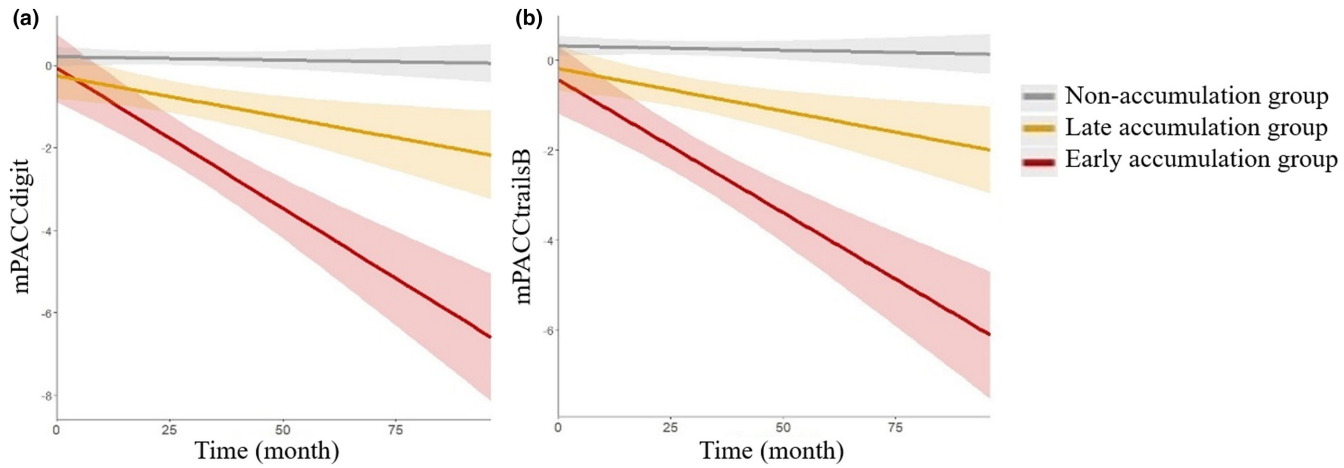

FIGURE 2 Longitudinal changes in the outcomes of the neuropsychological tests amongst the three Aβ trajectory groups. The *y*-axis represents the predicted (a) mPACCdigit and (b) mPACCtrailsB scores for each follow-up month derived from a predicted model equation using a linear mixed effect model. mPACCdigit, modified Preclinical Alzheimer's Cognitive Composite with digit symbol substitution; mPACCtrailsB, modified Preclinical Alzheimer's Cognitive Composite with trails B.

development set). The proportion of *APOE ε4* carriers and females in the validation set did not differ significantly from those in the development set (*APOE ε4*, 33.1% vs. 30.1%, $p=0.438$; female, 56.4% vs. 52.5%, $p=0.457$). To investigate the number of latent classes for the validation set, the BIC, SSBIC, LMR-LRT, BLRT and entropy were comprehensively considered. All class 2 or 3 models had high entropy. The goodness of fit for each of the class 3 models, compared to the class 2 model, was statistically significant, suggesting that the class 3 model would be adequate (L/L/L, BLRT $p<0.001$; LMR-LRT, $p=0.015$; L/Q/L, BLRT $p<0.001$; LMR-LRT $p=0.012$). The difference of the BIC (or SSBIC) value between the L/L/L class 3 model and the L/Q/L class 3 model was small (<2), indicating that the L/L/L and L/Q/L models have similar model performance. Thus, similar to the development set, the simpler model (L/L/L) was selected as the final model (Table S2).

Figure S1 shows the global Centiloid trajectories for the class 3 model. Class 1, comprising an estimated 60.9% of the participants, showed a pattern resembling the non-accumulation group, maintaining a low Aβ burden (intercept 4.351, SE = 1.563, $p=0.005$; linear slope 0.082, SE = 0.237, $p=0.728$; Table S3). Class 2, consisting of an estimated 18.8% of the participants, was initially characterized by an increase in Aβ levels during the same period at a relatively low baseline level, similar to the late accumulation group (intercept 31.739, SE = 5.180, $p<0.001$; linear slope 2.744, SE = 0.505, $p<0.001$). Class 3, which included an estimated 20.3% of the participants, had a baseline value of 107.824, higher than that of the other classes, and consistently exhibited high Aβ levels (intercept 107.824, SE = 7.405, $p<0.001$; linear slope 1.136, SE = 0.719, $p=0.114$), comparable to the early accumulation group. The results of LCGA in the external validation set were comparable to those in the development set.

DISCUSSION

In the present study, a class 3 model was developed to identify the distinct patterns in Aβ trajectories amongst CU older individuals using the LCGA technique. Our major findings are as follows. First, the optimal model was the class 3 model (L/L/L), consisting of the non-accumulation, late accumulation and early accumulation groups. Second, the proportion of *APOE ε4* carriers increased from the

non-accumulation group to the late accumulation and early accumulation groups. Third, the group with early accumulation displayed the most notable longitudinal decrease, followed by the late accumulation group, in comparison to the non-accumulation group, despite no significant differences in cognitive function amongst the participants in the three groups at baseline. Taken together, our findings indicate that CU older individuals can be classified into three distinct groups based on their Aβ trajectory patterns, with varying prognoses of cognitive decline across groups. These results have important implications for establishing personalized treatment and prevention strategies for CU older individuals in clinical practice.

Our first major finding was the establishment of a class 3 (L/L/L) model based on changes in AV45 PET SUVR amongst CU older populations. These findings were also validated in an independent cohort from Samsung Medical Centre, where LCGA analysis also indicated that the class 3 model was the most adequate for Aβ trajectories. These results are in line with those from previous studies that showed distinct trajectories of cognitive change or functional decline amongst subjective memory complainers in preclinical patients with AD [10, 24, 25]. Although these studies have advantages as longitudinal observational studies, our approach using LCGA to identify distinct trajectories of longitudinal Aβ accumulation would be more helpful in the biomarker-based field and may lead to the development of personalized prevention strategies. Furthermore, rather than a longitudinal data analysis using a prior baseline classification, our qualitatively distinct trajectories were identified based on time-varying changes in Aβ accumulation.

Our second major finding was that the prevalence of *APOE ε4* carriers increased from the non-accumulation to the late accumulation and early accumulation groups, despite the lack of baseline cognitive differences amongst individuals in these groups. The *APOE ε4* allele is a well-established risk factor for Aβ deposition in the brain [26–28]. Our findings align with those from earlier studies in showing that the prevalence of Aβ plaques correlates with ageing and the presence of the *APOE ε4* allele in clinically non-demented individuals [29–31]. Cognitively healthy *APOE ε4* carriers can develop medial temporal atrophy [32] and cognitive decline at faster rates than non-carriers [33]. Our results show that even in CU older individuals the presence of *APOE ε4* may lead to Aβ accumulation over time, thus emphasizing the need for early screening and intervention for AD in *APOE ε4* carriers.

Our final major finding was that progressive cognitive decline characterized the late accumulation and early accumulation groups compared to the non-accumulation group. Whilst few studies have shown a higher prevalence of cognitive impairment in Aβ-positive CU individuals than in Aβ-negative individuals [34, 35], the influence of the trajectory of Aβ deposition on prognosis remains unclear. Our findings demonstrate longitudinal cognitive changes according to distinct Aβ trajectories, consistent with a previous LCGA study that a higher Aβ load is associated with lower cognitive performance amongst subjective memory complainers [10]. Additionally, the AV45 PET SUVR of 1.095 at baseline in the late accumulation group, which was below the cutoff value of 1.11 suggested by the ADNI cohort [36], indicates Aβ negativity. However, SUVR in the late accumulation group gradually increased over time, eventually showing Aβ positivity. Recent evidence indicates that subthreshold Aβ deposition results in future cognitive decline and the accumulation of AD pathology, including tau protein accumulation [37–39]. Therefore, even amongst CU older populations, evaluating and continuously monitoring Aβ pathology are crucial for prognosis and early prevention. Whilst Aβ PET SUVR monitoring is impractical due to high cost and limited accessibility, plasma biomarkers may offer a promising alternative. Future studies applying LCGA to plasma biomarkers may provide valuable insights into disease progression in CU older populations.

The early accumulation group exhibited a significant decrease in HV over time compared to the non-accumulation group. Hippocampal atrophy has been validated as a neurodegeneration biomarker of AD based on the 2018 National Institute on Aging and Alzheimer's Association research framework [1]. Even in individuals with normal cognitive performance, those with elevated Aβ accumulation may develop more dramatic neurodegenerative changes, leading to subsequent longitudinal cognitive decline, than those without Aβ burden. These findings underscore that advanced preclinical AD is associated with Aβ deposition and HV reduction [40–42], emphasizing the potential clinical relevance of early detection and intervention in preclinical AD.

Limitations

The strength of this study is that an optimal class 3 model based on LCGA was developed, revealing distinct Aβ trajectory patterns in CU older individuals. However, several limitations are also noted. First, our study lacks information about tau protein accumulation. Future LCGA studies can explore heterogeneous trajectories of tau changes or the combined effects of Aβ and tau changes with longitudinal changes in tau PET. Second, although the trajectories were based on global SUVR, the potential influence of partial volume effects cannot be completely excluded. Future studies should consider partial volume correction to enhance the accuracy of PET data interpretation. Finally, besides AD, other pathologies, including Lewy body and transactive response DNA-binding protein pathologies, hippocampal sclerosis, argyrophilic grain disease and cerebrovascular diseases, may be associated with neurodegeneration and cognitive decline. Nevertheless, our study is noteworthy in that the presence of distinct Aβ trajectories amongst CU older adults were revealed and also modulations in the longitudinal patterns of cognitive decline according to the Aβ trajectories.

CONCLUSIONS

In this study, LCGA was used to identify distinct trajectories of Aβ changes in CU older individuals and showed that the severity of longitudinal cognitive decline differs depending on the Aβ trajectories.

These findings may enhance our understanding of the heterogeneity of Aβ accumulation in CU older populations and may be helpful for the early diagnosis and implementation of strategies for disease-modifying therapy and prevention in preclinical AD.

AUTHOR CONTRIBUTIONS

Young Ju Kim: Conceptualization; formal analysis; writing – original draft. **Jihwan Yun:** Conceptualization; writing – original draft; formal analysis. **Sang Won Seo:** Methodology. **Jun Pyo Kim:** Methodology. **Hyemin Jang:** Writing – review and editing. **Hee Jin Kim:** Writing – review and editing. **Duk L. Na:** Writing – review and editing. **Sookyoung Woo:** Supervision. **Min Young Chun:** Conceptualization; writing – original draft; formal analysis; supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT

The dataset is owned by a third-party organization, the Alzheimer's Disease Neuroimaging Initiative (ADNI). The datasets generated during the study are available at http://adni.loni.usc.edu/data-samples/access-data/.

ETHICS STATEMENT

ADNI met all ethical standards in the collection of data. The Ethics Committees/Institutional Review Boards that approved the ADNI study are Albany Medical Center Committee on Research Involving Human Subjects Institutional Review Board, Boston University Medical Campus and Boston Medical Center Institutional Review Board, Butler Hospital Institutional Review Board, Cleveland Clinic Institutional Review Board, Columbia University Medical Center Institutional Review Board, Duke University Health System Institutional Review Board, Emory Institutional Review Board, Georgetown University Institutional Review Board, Health Sciences Institutional Review Board, Houston Methodist Institutional Review Board, Howard University Office of Regulatory Research Compliance, Icahn School of Medicine at Mount Sinai Program for the Protection of Human Subjects, Indiana University Institutional Review Board, Institutional Review Board of Baylor College of Medicine, Jewish General Hospital Research Ethics Board, Johns Hopkins Medicine Institutional Review Board, Lifespan–Rhode Island Hospital Institutional Review Board, Mayo Clinic Institutional Review Board, Mount Sinai Medical Center Institutional Review Board, Nathan Kline Institute for Psychiatric Research and Rockland Psychiatric Center Institutional Review Board, New York University Langone Medical Center School of Medicine Institutional Review Board, Northwestern University Institutional Review Board, Oregon Health and Science University Institutional Review Board, Partners Human Research Committee Research Ethics Board Sunnybrook Health Sciences Centre, Roper St Francis Healthcare Institutional Review Board, Rush University Medical Center Institutional Review Board, St Joseph's Phoenix Institutional Review Board, Stanford Institutional Review Board, Ohio State University Institutional Review Board, University Hospitals Cleveland Medical Center Institutional Review Board, University of Alabama Office of the IRB, University of British Columbia Research Ethics Board, University of California Davis Institutional Review Board Administration, University of California Los Angeles Office of the Human Research Protection Program, University of California San Diego Human Research Protections Program, University of California San Francisco Human Research Protection Program, University of Iowa Institutional Review Board, University of Kansas Medical Center Human Subjects Committee, University of Kentucky Medical Institutional Review Board, University of Michigan Medical School Institutional Review Board, University of Pennsylvania Institutional Review Board, University of Pittsburgh Institutional Review Board, University of Rochester Research Subjects Review Board, University of South Florida Institutional Review Board, University of Southern California Institutional Review Board, UT Southwestern Institution Review Board, VA Long Beach Healthcare System Institutional Review Board, Vanderbilt University Medical Center Institutional Review Board, Wake Forest School of Medicine Institutional Review Board, Washington University School of Medicine Institutional Review Board, Western Institutional Review Board, Western University Health Sciences Research Ethics Board and Yale University Institutional Review Board. ADNI protocol and ethics statement: http://adni.loni.usc.edu/wp-content/themes/freshnews-dev-v2/documents/clinical/ADNI-2_Protocol.pdf. The institutional review board of Samsung Medical Centre approved the study protocol, and written informed consent was obtained from participants and their caregivers.

CONSENT

Informed written consent was obtained from all participants at each site of the ADNI study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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