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RESEARCH ARTICLE

Age-related amyloid beta dynamics modeled with the generalized additive model for location, scale, and shape (GAMLSS) across diverse populations: Cross-sectional trajectories and longitudinal validation

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Abstract

INTRODUCTION: We developed and validated age-related amyloid beta (Aβ) positron emission tomography (PET) trajectories using a statistical model in cognitively unimpaired (CU) individuals.

Sungjoo Lee and Min Young Chun contributed equally to this study and share first authorship.

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METHODS: We analyzed 849 CU Korean and 521 CU non-Hispanic White (NHW) participants after propensity score matching. Aβ PET trajectories were modeled using the generalized additive model for location, scale, and shape (GAMLSS) based on baseline data and validated with longitudinal data. Subgroup analyses examined apolipoprotein E (*APOE*) ε4 and sex effects.

RESULTS: Age-related centile curves of Aβ PET Centiloid values showed stable distributions in the lower percentiles, increasing with age in the upper percentiles. NHWs exhibited steeper Aβ accumulation trajectories, particularly among *APOE* ε4 carriers. Calibration with longitudinal data confirmed the reliability of this cross-sectional method.

DISCUSSION: We developed a statistical model of age-related Aβ PET trajectories using baseline data, validated with longitudinal data. NHWs exhibited steeper trajectories than Koreans, suggesting population-specific differences in Aβ accumulation.

KEYWORDS
amyloid beta, amyloid beta positron emission tomography trajectories, Centiloid scale, ethnic differences, generalized additive model for location, scale, and shape, positron emission tomography

Highlights

- A generalized additive model for location, scale, and shape model was applied to examine age-related amyloid beta (Aβ) trajectories with baseline data.
- Trajectories were validated using longitudinal data, confirming model reliability.
- Non-Hispanic Whites exhibited steeper trajectories than Koreans, especially in apolipoprotein E ε4 carriers.
- Our approach enables scalable modeling of Aβ dynamics for Alzheimer's disease prevention strategies.
- Findings highlight the importance of multi-ethnic research in Aβ accumulation.

1 | BACKGROUND

Alzheimer's disease (AD) is characterized by the abnormal accumulation of amyloid beta (Aβ) plaques and tau tangles, which drive neurodegeneration and cognitive decline. Among these pathological changes, Aβ deposition begins decades before clinical symptoms appear, making it a critical target for early detection and intervention. Even in cognitively unimpaired (CU) individuals, Aβ plaques are frequently observed, and the prevalence of Aβ plaques increases with age. However, while it is well documented that Aβ positivity increases with advancing age,[1–4] few studies have focused on characterizing age-related Aβ trajectories in CU individuals.[5,6]

Longitudinal age-related Aβ trajectories in CU individuals provide vital insights into disease progression, helping identify individuals at high risk for AD, and informing both primary and secondary prevention strategies. Previous studies have predominantly used longitudinal data with various statistical approaches, including individual-level linear regression, linear mixed-effect models, or group-based trajectory models.[1] For example, an Aβ chronicity modeling approach uses group-based trajectory modeling (GBTM) to identify subgroups with similar Aβ accumulation patterns.[3,5] However, these approaches require extensive longitudinal data collected over many years, which is often impractical—particularly in CU populations—and also rely on predefining the number of subgroups. To address these limitations, some studies have used short-term follow-up data to approximate 10- to 20-year trajectories.[7,8] One cross-sectional study attempted to estimate longitudinal Aβ trajectories; however, it may lack the flexibility needed to capture the complex patterns of Aβ deposition, particularly given the skewed distributions and heteroscedasticity across different age groups.[9] An alternative approach is the generalized additive model for location, scale, and shape (GAMLSS),[10,11] which has been widely used to model pediatric growth curves. GAMLSS estimates multiple parameters of a distribution—location (mean), scale (variability), skewness, and kurtosis—as functions of age. This enables the construction of age-related centile curves, which describe how a biomarker is distributed across percentiles (e.g., 10th, 50th, and 90th) at each age. Centile curves based on Aβ positron emission tomography (PET) values provide a detailed view of age-related changes in Aβ burden,

facilitating the identification of individuals with accelerated or atypical accumulation across the population distribution. GAMLSS thus offers a flexible framework for modeling non-linear, non-normal distributions using baseline data and accommodating age-specific variation.

Age-related Aβ trajectories might be influenced by several factors, including sex and genetic risk.[12–14] While sex differences in AD prevalence and cognitive decline—higher prevalence and faster progression in females—are well established, their impact on Aβ accumulation remains controversial. In addition to sex effects, the apolipoprotein E (*APOE*) ε4 allele, the strongest genetic risk factor for late-onset AD, accelerates Aβ deposition and contributes to individual variability in accumulation patterns.[15–17] These differences underscore the need for models that account for such factors when assessing Aβ trajectories.

Compared to non-Hispanic White (NHW) cohorts,[6,18] CU individuals of African American[19,20] and East Asian[21,22] descent often exhibit lower rates of Aβ positivity, even after accounting for sex and *APOE* ε4 effects. These differences may reflect differences in genetic, environmental, and lifestyle factors. These differences highlight the importance of studying diverse populations to ensure findings are generalizable and inform targeted prevention strategies.

The goal of this study was to use GAMLSS to develop age-related Aβ trajectories for CU individuals using baseline data from a Korean cohort and to validate these trajectories with longitudinal follow-up data. To test the hypothesis that there are differences between the Korean and NHW cohort, we then applied the same methods using data from the United States–based Alzheimer's Disease Neuroimaging Initiative (ADNI). We further examined whether the observed patterns were replicated in an independent CU cohort from the Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) Study.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed literature from traditional sources and cohort studies on models for age-related amyloid beta (Aβ) accumulation trajectories. Most studies relied on longitudinal data, with few using cross-sectional approaches. While the generalized additive model for location, scale, and shape (GAMLSS) has been applied in pediatric growth modeling, it has not been used for Aβ accumulation patterns.
2. **Interpretation**: This study applied GAMLSS-based centile estimation to model Aβ trajectories from baseline data, validated with longitudinal data. Comparison of Korean and non-Hispanic White (NHW) cohorts revealed steeper age-related Aβ trajectories in NHWs. Replication analysis using the A4 Study supported the robustness of our findings. These results underscore the importance of multi-ethnic research in refining population-specific Alzheimer's disease prevention strategies.
3. **Future directions**: This modeling framework should be expanded to diverse populations to enhance prediction of progression. Future studies should integrate multi-omics approaches to explore mechanisms underlying ethnic differences in Aβ dynamics.

2 | METHODS

2.1 | Study design and population

A total of 5125 Korean participants were recruited from the Korea Registries to Overcome Dementia and Accelerate Dementia Research Project (K-ROAD),[23] a member of the worldwide ADNI. All participants underwent comprehensive neuropsychological assessments, brain magnetic resonance imaging (MRI), and Aβ PET imaging. CU status was defined based on the following criteria: (1) no medical history likely to affect cognitive function, as per Christensen's health screening criteria[24] and (2) no objective cognitive impairment on any cognitive domain, assessed using a comprehensive neuropsychological test battery and operationalized as performance above −1.0 standard deviations (SD) of age- and education-adjusted norms in memory, and above −1.5 SD in other cognitive domains.[25] After applying these criteria, 996 CU Korean participants aged ≥ 50 years at baseline and with baseline Aβ PET scans were included for model development. Of these, 149 participants underwent at least one follow-up scan, which was used for internal validation.

To compare age-related Aβ accumulation patterns across ethnicities, we analyzed data from the North America ADNI (NA-ADNI) dataset. From this cohort, we identified 555 CU NHW participants, aged ≥ 50 years at baseline, who contributed a total of 1446 longitudinal measurements (including 891 follow-ups). Detailed inclusion and exclusion criteria for NA-ADNI are available on the ADNI website (http://www.adni-info.org). A flow diagram illustrating participant selection is presented in Figure S1 in supporting information.

To further evaluate the replicability of our findings, we incorporated data from the A4 Study as an independent NHW cohort. Specifically, we compared age-related Aβ trajectories between NHW participants from NA-ADNI and those from the A4 Study. The cohort-specific CU definitions and inclusion criteria for K-ROAD, NA-ADNI, and the A4 Study are summarized in Table S1 in supporting information.

All K-ROAD participants provided written informed consent, and the institutional review board of each participating center approved the study protocol. Additionally, the ADNI Data Sharing and Publications Committee approved data use and publication.

2.2 | Amyloid PET imaging acquisition

All Korean participants underwent Aβ PET scans using either [^{18}F]-florbetaben, [^{18}F]-flutemetamol, or [^{11}C]-Pittsburgh compound B, following the manufacturer's guidelines (Method S1 in supporting

information). For the K-ROAD cohort, all imaging analyses, including the calculation of standardized uptake value ratios (SUVRs), were performed at the core laboratory of Samsung Medical Center. All NA-ADNI participants from the NA-ADNI cohort and A4 Study participants underwent [^{18}F]-florbetapir (AV45) PET scans, and SUVRs were obtained from their respective datasets.

To ensure comparability of Aβ PET measurements across different tracers, we used the Klunk Centiloid (CL) scale, which is widely accepted in cohort studies and clinical trials.[26–30] Detailed procedures for obtaining SUVRs and converting these values to CL in the K-ROAD study are provided in Method S1. For the NA-ADNI participants, we converted AV45 SUVRs to CL values using the previously established linear transformation (CL = 188.22 × SUVR_FBP – 189.16).[26,27]

2.3 | Propensity score matching and stratification for comparative analysis of Aβ accumulation patterns

Only baseline data (i.e., data from each participant's first visit) were used to fit the models, and the fitted models were subsequently validated using the remaining longitudinal data from the same subjects. Prior to model fitting, propensity score matching (PSM) was performed to balance potential confounding factors between the two cohorts. Before matching, the total cohort consisted of 1551 participants, including 996 (64.2%) Koreans and 555 (35.8%) NHWs. NHWs exhibited a higher proportion of males and *APOE* ε4 carriers, as well as higher age and CL values compared to Koreans, indicating baseline imbalance between the groups. To address this imbalance, we conducted 1:2 PSM using a multivariable logistic regression model, with age, sex, and *APOE* ε4 status (carriers and non-carriers) as covariates. The nearest neighbor algorithm without replacement was applied, using a caliper width of 0.1 SD of the logit of the propensity score. After PSM, a total of 1370 participants (849 from K-ROAD and 521 from NA-ADNI) were included (Figure 1). The quality of matching was assessed by the absolute standardized mean difference (aSMD), with variables exhibiting an aSMD < 0.1 considered well balanced. Baseline characteristics of the propensity score (PS)–matched participants were summarized as: means with SD or medians with interquartile ranges for continuous variables (e.g., age), and as counts with percentages for categorical variables (e.g., sex, *APOE* ε4 status).

To further explore potential ethnic differences in CL accumulation patterns, the PS-matched cohort underwent a two-stage stratification process. First, the PS-matched cohort was stratified by *APOE* ε4 carrier status (carriers vs. non-carriers) and sex (male vs. female) to form subgroups. Subsequently, both the overall matched cohort and the newly formed subgroups were each stratified by ethnicity. As a result, a total of 10 different datasets were generated for analysis: Koreans versus NHWs in (1) the total PS-matched cohort, (2) *APOE* ε4 carriers, (3) *APOE* ε4 non-carriers, (4) males, and (5) females (Figure 1).

2.4 | Centile curves and model fitting for Aβ trajectories

Growth curves based on centile estimation[31] were constructed to illustrate the distribution of CL values as a function of age. This approach was applied separately to each ethnic group in the total PS-matched cohort, as well as to subgroups defined by *APOE* ε4 status and sex, to compare age-related trajectories of CL accumulation between Koreans and NHWs. For centile estimation of CL, we used GAMLSS.[10,11] Within GAMLSS, the lambda–mu–sigma method was extended with a sinh–arcsinh distribution to take account of skewness and kurtosis of the CL values accounting for negative and near-zero observations. Penalized spline functions[32] were applied to model four parameters as smooth functions of age: μ (location shift parameter), σ (scaling parameter), ν (skewness parameter), and τ (kurtosis parameter). Two versions of sinh–arcsinh distribution were applied: the original sinh–arcsinh distribution and the modified sinh–arcsinh distribution.[33] Model selections were conducted with the Akaike information criterion[34] and Schwarz–Bayesian criterion[35] to select the appropriate distribution of CL. Goodness of fit of models was assessed with worm plots, which are detrended quantile–quantile plots of the residuals.[36]

2.5 | Model validation and statistical analysis framework

Model validation was conducted by comparing the observed longitudinal CL values to those predicted by the fitted models. To predict longitudinal CL values, we first determined each participant's percentile position based on the baseline observation, then estimated their CL values at follow-up ages using the estimated trajectory of the corresponding percentile. The root mean square error (RMSE) was calculated to assess the overall prediction performance. The agreement between observed and predicted values was further evaluated using calibration plots, with smoothed curves fitted using locally estimated scatterplot smoothing (LOESS).[37] Linear regression model of the form $Y_i = \alpha + \beta \hat{Y}_i$ was fitted to derive calibration performance by estimating the calibration slope ($\hat{\beta}$; ideal value of 1) and calibration-in-the-large (intercept, $\hat{\alpha}$; ideal value of 0), along with their 95% confidence intervals (CIs).[37]

Additionally, we assessed whether Aβ accumulation patterns of NHWs from NA-ADNI were replicated in NHWs from the independent A4 Study. To ensure comparability between cohorts, an additional PSM in a 1:4 ratio was performed between the pre-matched NHWs from NA-ADNI and NHWs from the A4 Study. The PSM procedure was identical to that previously applied between the Koreans from K-ROAD and NHWs from NA-ADNI. Subsequently, centile curves were estimated to the matched A4 Study cohort. As in Figure 1, five datasets were generated for analysis: NHWs from the A4 Study in (1) the total PS-matched cohort, (2) *APOE* ε4 carriers, (3) *APOE* ε4 non-carriers, (4) males, and (5) females.

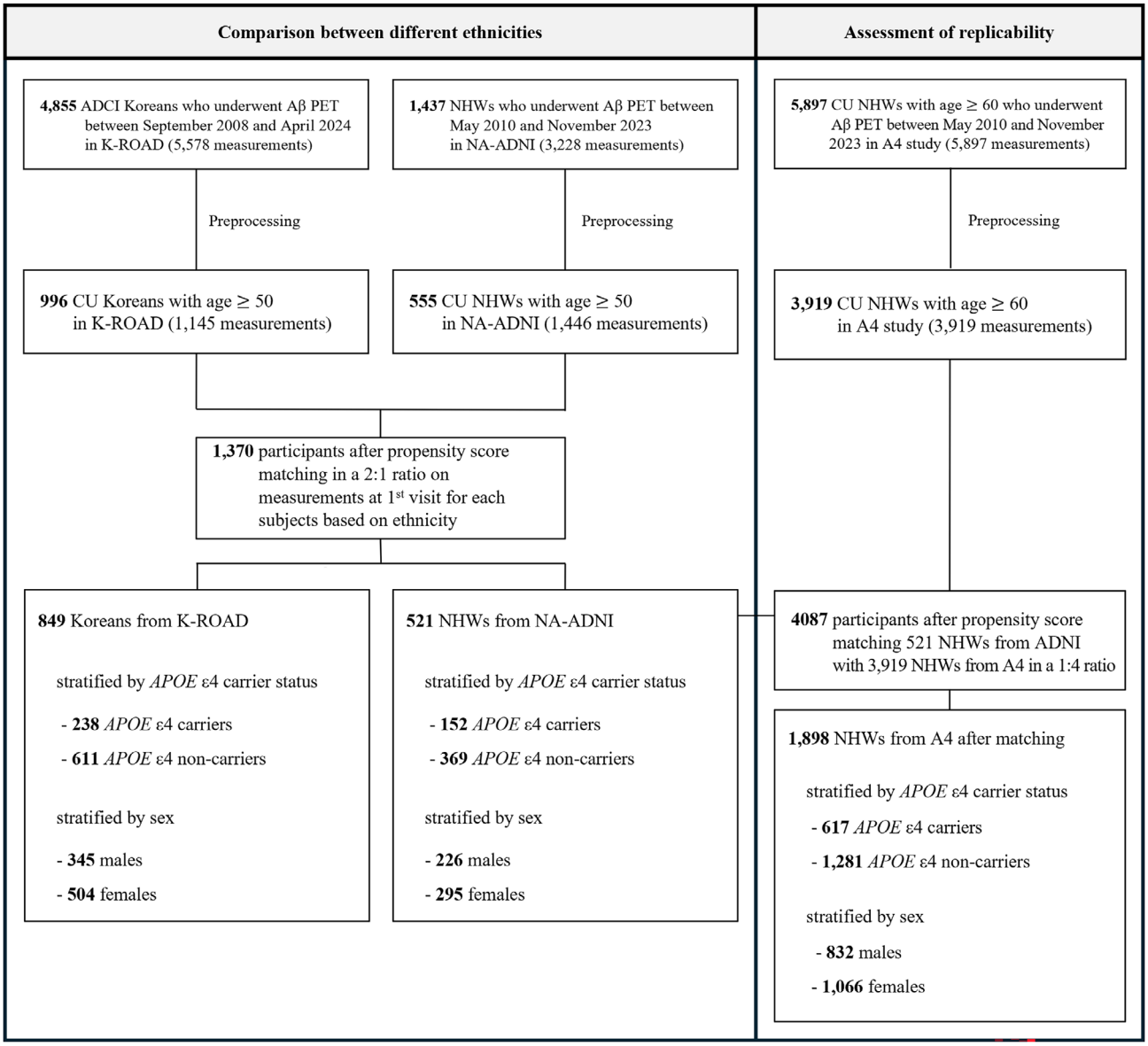

FIGURE 1 Study flow chart. A4, Anti-Amyloid Treatment in Asymptomatic Alzheimer's Study; Aβ, amyloid beta; ADCI, Alzheimer's disease-type cognitively impaired; *APOE*, apolipoprotein E; CU, cognitively unimpaired; NA-ADNI, North American Alzheimer's Disease Neuroimaging Initiative; NHW, non-Hispanic White; PET, positron emission tomography.

All analyses were performed using R version 4.4.0 (The R Foundation, http://www.R-project.org). Model fitting and diagnostic procedures were conducted with the GAMLSS package version 5.4-22. The pb () function in R was applied as the non-parametric smoothing function, and both SASHo(μ,σ,ν,τ) and SASH(μ,σ,ν,τ) distributions were considered. A two-sided P value < 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics of participants

After PSM, a total of 1370 participants (849 Koreans and 521 NHWs) were included. In the PS-matched cohort, 345 (40.6%) of Koreans and 226 (43.4%) of NHWs were male, while 238 (28.0%) of Koreans and 152 (29.2%) of NHWs carried at least one *APOE ε4* allele. The mean (SD) follow-up duration was 5.82 (1.80) years for Koreans and 7.80 (3.04) years for NHWs from NA-ADNI. Baseline characteristics before PSM are summarized in Table S2 in supporting information. The total PS-matched cohort (Table 1) and all subgroups (Tables S3 and S4 in supporting information) were well balanced between the two ethnic groups across all variables. Although aSMD for age in total PS-matched cohort was slightly elevated (0.321), the age distributions remained comparable between ethnicities, with similar mean age values (mean ± SD, 72.5 ± 6.5 years for Koreans vs. 72.9 ± 6.3 years for NHWs) and the median ages (73.0 vs. 72.2 years), suggesting minimal residual imbalance. Overall, aside from this modest difference in age, PSM successfully minimized baseline disparities, ensuring a comparable foundation for subsequent analyses.

TABLE 1 Baseline characteristics of the propensity score–matched cohorts.

Variables	Koreans (K-ROAD)	NHWs (NA-ADNI)	NHWs (A4 Study[a])	aSMD[b] Koreans vs. NHWs (NA-ADNI)	aSMD[b] NHWs (NA-ADNI) vs. NHWs (A4 Study)
	(*n* = 849)	(*n* = 521)	(*n* = 1898)		
Age, years					
Mean ± SD	72.5 ± 6.5	72.9 ± 6.3	72.5 ± 5.2	0.009	0.070
Median [range]	73.0 [68.0, 77.0]	72.2 [67.7, 77.1]	71.6 [68.0, 76.2]		
Male, n (%)	345 (40.6)	226 (43.4)	832 (43.8)	0.020	0.009
APOE ε4 carriers, *n* (%)	238 (28.0)	152 (29.2)	617 (32.5)	0.024	0.072
APOE genotype, *n* (%)					
ε2/ε2	8 (0.9)	1 (0.2)	16 (0.8)	0.007	0.007
ε2/ε3	77 (9.1)	58 (11.1)	196 (10.3)	0.025	0.008
ε2/ε4	11 (1.3)	9 (1.7)	44 (2.3)	0.001	0.006
ε3/ε3	526 (62.0)	310 (59.5)	1069 (56.3)	0.006	0.032
ε3/ε4	194 (22.9)	131 (25.1)	530 (27.9)	0.004	0.028
ε4/ε4	33 (3.9)	12 (2.3)	43 (2.3)	0.021	0.0004

Abbreviation: A4, Anti-Amyloid Treatment in Asymptomatic Alzheimer's Study; *APOE*, apolipoprotein E; aSMD, absolute standardized mean difference; K-ROAD, Korea Registries to Overcome Dementia and Accelerate Dementia Research Project; NA-ADNI, North America Alzheimer's Disease Neuroimaging Initiative; NHW, non-Hispanic White; SD, standard deviation.

[a]The A4 cohort was used for assessment of replicability.

[b]aSMD represents the absolute standardized mean difference between Koreans and NHWs from NA-ADNI, and between NHWs from NA-ADNI and NHWs from the A4 Study.

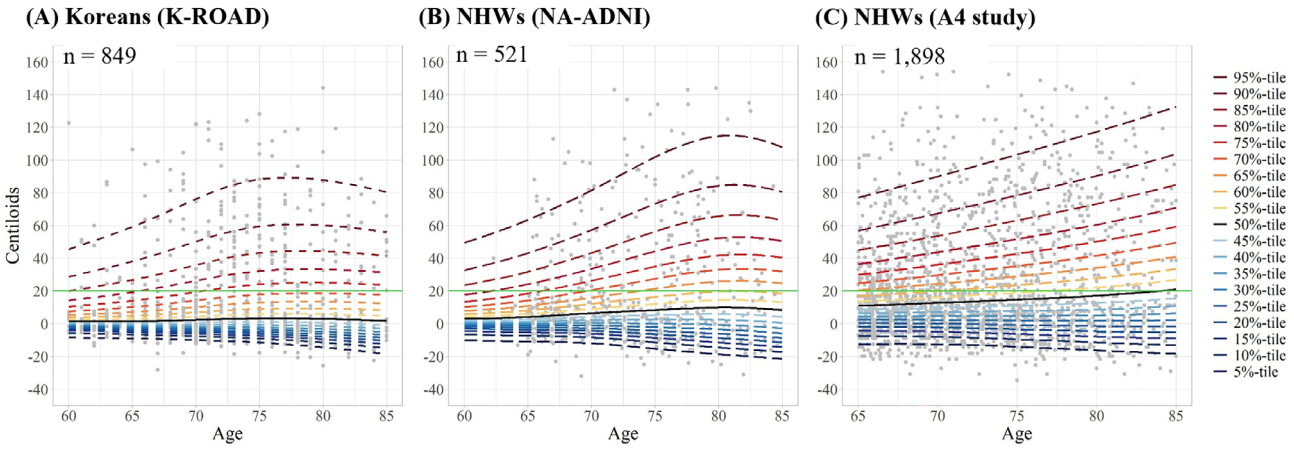

FIGURE 2 Estimated centile curves of Aβ PET Centiloid values by age in cognitively unimpaired Koreans from K-ROAD, NHWs from NA-ADNI, and NHWs from the A4 Study. Steeper increases in the upper centile curves indicate accelerated Aβ accumulation with advancing age. Compared to Koreans, both NHW cohorts showed more pronounced upward trends in the higher percentiles, suggesting faster accumulation in individuals with high Aβ burden. Percentiles from 5 to 95e (in 5% increments) are depicted as dashed lines, with the 50th percentile (median) shown as a solid black line. Gray dots represent observed individual-level Centiloid values. Upper percentiles are displayed in red tones, and lower percentiles in blue tones. A4, Anti-Amyloid Treatment in Asymptomatic Alzheimer's Study; Aβ, amyloid beta; K-ROAD, Korea Registries to Overcome Dementia and Accelerate Dementia Research Project; NA-ADNI, North American Alzheimer's Disease Neuroimaging Initiative; NHW, non-Hispanic White; PET, positron emission tomography.

3.2 | The pattern of Aβ accumulation

The estimated age-related centile curves of CL values for Koreans and NHWs from NA-ADNI—matched for sex and *APOE* ε4 status—are shown in Figure 2A,B, respectively. In both groups, the lower percentiles (5th–25th) remain relatively flat across age, suggesting little or no Aβ accumulation among individuals with low baseline burden. In contrast, the upper percentiles (75th–95th) increase steadily with age, indicating progressive Aβ accumulation in individuals with higher baseline levels. Notably, NHWs from NA-ADNI exhibit steeper increases

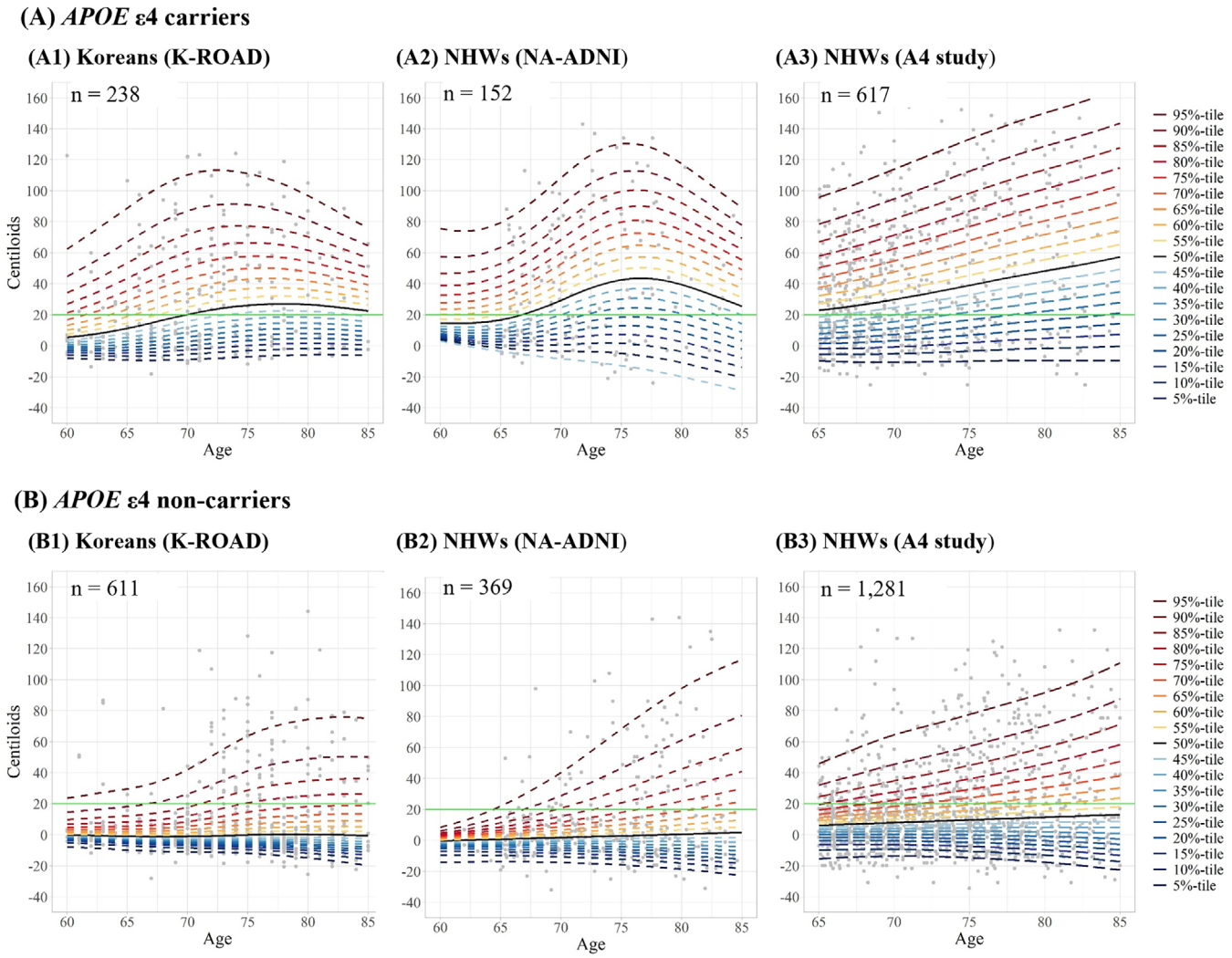

FIGURE 3 Estimated centile curves of Aβ PET Centiloid values stratified by *APOE* ε4 carrier status and ethnicity. All ε4 carrier groups (A1–A3) exhibit progressive age-related increases in Aβ accumulation, particularly from the 40th percentile and above. Notably, both NHW cohorts (A2 and A3) demonstrate substantially steeper increases compared to Koreans ε4 carriers (A1), indicating accelerated Aβ accumulation in NHW ε4 carriers. In contrast, ε4 non-carriers (B1–B3) display only modest age-related increases, with minimal ethnic differences observed below the 75th percentile. Age-related increases are primarily observed in the upper percentiles (75th–95th). Although the A4 Study (A3 and B3) shows generally higher Centiloid values than the NA-ADNI cohort (A2 and B2), the overall trajectory patterns remain comparable. As in Figure 2, the centile curves depict the distribution of Aβ burden by age across percentiles. A4, Anti-Amyloid Treatment in Asymptomatic Alzheimer's Study; Aβ, amyloid beta; *APOE*, apolipoprotein E; K-ROAD, Korea Registries to Overcome Dementia and Accelerate Dementia Research Project; NA-ADNI, North American Alzheimer's Disease Neuroimaging Initiative; NHW, non-Hispanic White; PET, positron emission tomography.

above the 50th percentile than Koreans, suggesting faster Aβ accumulation with advancing age. The NHWs from the A4 Study show slightly higher CL values relative to NA-ADNI; however, both NHW cohorts demonstrate similar age-related accumulation trajectories (Figure 2C).

3.3 | Age-related centile curves of CL according to *APOE* ε4 status

Figure 3 shows the estimated age-specific centile trajectories of CL values, stratified by *APOE* ε4 status (carriers and non-carriers; Figure 3A1 and 3B1 for Koreans, Figure 3A2 and 3B2 for NHWs from NA-ADNI, and Figure 3A3 and 3B3 for NHWs from the A4 Study). In both ε4 carriers and non-carriers, the upper percentiles (75th–95th percentiles) exhibit more pronounced age-related increases compared to lower centiles, indicating faster Aβ accumulation in individuals with higher baseline burden. This pattern is particularly more pronounced among ε4 carriers, with NHWs showing steeper increases compared to Koreans from the 40th percentile upward. Notably, the age-dependent accumulation patterns observed in NA-ADNI were replicated in the independent A4 Study, despite slightly higher baseline CL values in the A4 Study across both ε4 carriers and non-carriers.

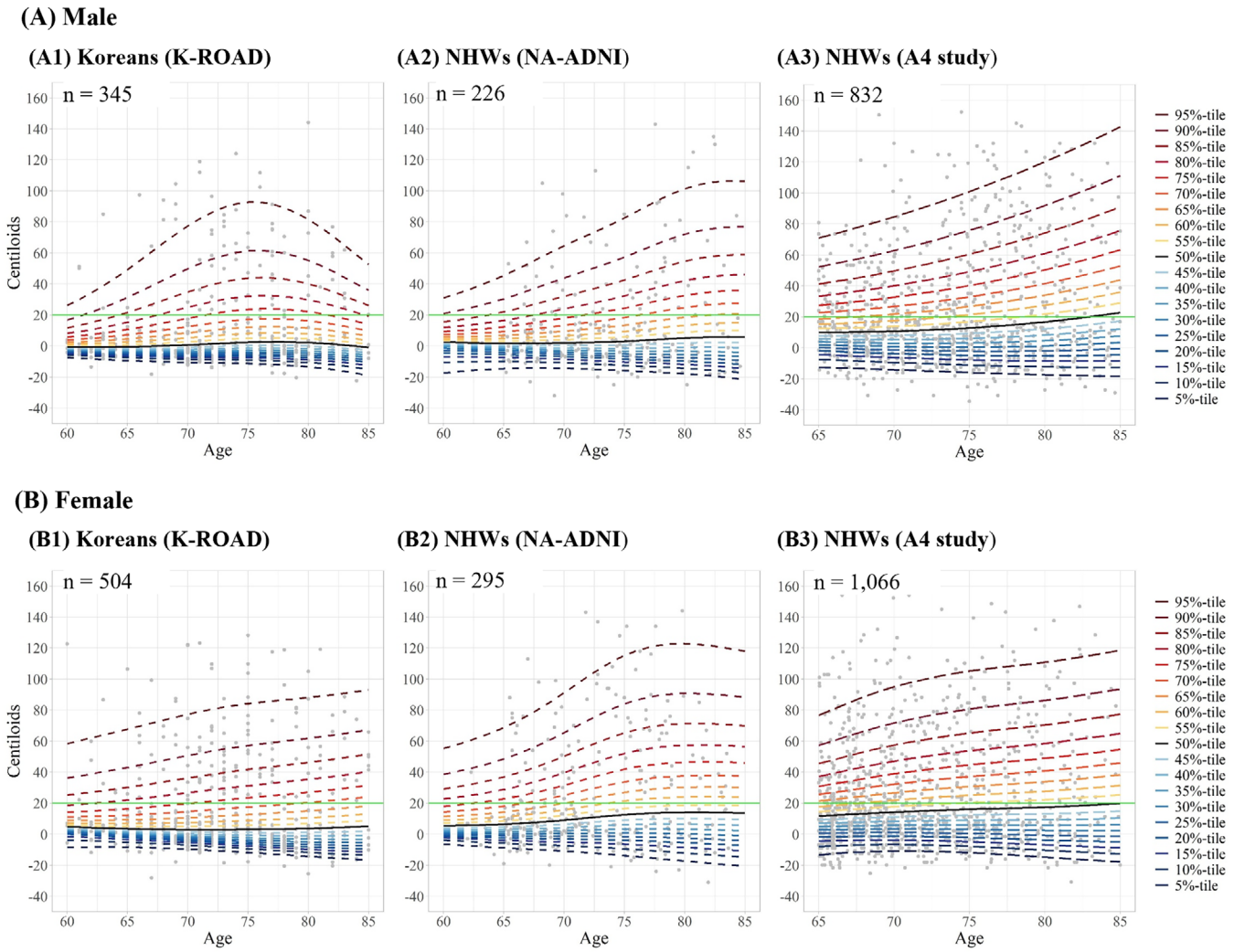

FIGURE 4 Estimated centile curves of Aβ PET Centiloid values stratified by sex and ethnicity. In both males and females, the centile curves show minimal increases below the 75th percentile across ethnic groups, with notable age-related Aβ accumulation confined to upper percentiles (75th–95th). NHWs from the A4 Study (A3 and B3) show slightly higher Centiloid values than those from NA-ADNI (A2 and B2); however, the overall trajectory patterns observed in NA-ADNI were replicated in the A4 Study for both sexes. These consistent findings across two NHW cohorts reinforce that NHWs exhibit higher Centiloid values and steeper Aβ accumulation trajectories than Koreans (A1 and B1). Percentile curves are interpreted as described in Figure 2. A4, Anti-Amyloid Treatment in Asymptomatic Alzheimer's Study; Aβ, amyloid beta; K-ROAD, Korea Registries to Overcome Dementia and Accelerate Dementia Research Project; NA-ADNI, North American Alzheimer's Disease Neuroimaging Initiative; NHW, non-Hispanic White; PET, positron emission tomography.

3.4 | Age-related centile curves of CL according to sex

Figure 4 presents the estimated age-related centile curves of CL values for Koreans and NHWs stratified by sex. In both males and females, age-related Aβ accumulation remains minimal below the 75th percentile across ethnic groups, with increases confined to the upper percentiles (75th–95th percentiles). Koreans exhibit relatively modest increases, while NHWs from NA-ADNI display steeper trajectories of CL progression, particularly among females in the upper percentiles (Figure 4B1 and 4B2). These patterns were consistent in an independent NHW cohort from the A4 Study, supporting the robustness of the observed ethnic differences. These findings suggest that sex does not substantially modify the ethnic differences in age-dependent Aβ accumulation patterns, as NHWs consistently present more pronounced increases in higher CL percentiles than Koreans.

3.5 | Validation of model calibration across ethnicities, *APOE* ε4 status, and sex

Korean participants demonstrated good calibration, with the slope approaching the ideal value of 1.0 (1.03, 95% CI; 0.97 to 1.09) and calibration-in-the-large close to 0 (1.99, 95% CI; −0.74 to 4.71). Similarly, analyses stratified by *APOE* ε4 status and sex also showed good calibration, indicating strong agreement between observed and pre-

TABLE 2 Model calibration assessed by comparing observed versus predicted Centiloid values.

	Centiloid[a]	Calibration slope[b]	Calibration-in-the-large[b]	RMSE
Koreans (K-ROAD)	14.02 (30.25)	1.03 (0.97, 1.09)	1.99 (−0.74, 4.71)	20.25
*APOE ε*4 carriers	30.64 (36.35)	1.15 (1.05, 1.25)	−0.72 (−6.84, 5.41)	24.24
*APOE ε*4 non-carriers	7.55 (24.67)	0.94 (0.85, 1.04)	2.37 (−1.29, 6.02)	17.44
Males	12.19 (29.80)	0.94 (0.84, 1.03)	2.22 (−2.57, 7.01)	16.15
Females	15.28 (30.52)	1.02 (0.93, 1.11)	3.68 (−0.79, 8.15)	21.81
NHWs (NA-ADNI)	18.87 (35.30)	1.00 (0.97, 1.03)	7.34 (6.02, 8.66)	13.07
*APOE ε*4 carriers	37.56 (40.19)	0.95 (0.88, 1.01)	12.39 (8.81, 15.97)	16.41
*APOE ε*4 non-carriers	11.17 (29.90)	0.94 (0.90, 0.98)	4.83 (3.48, 6.17)	14.41
Males	13.75 (32.27)	1.00 (0.96, 1.04)	6.39 (4.82, 7.96)	15.9
Females	22.80 (37.02)	1.00 (0.96, 1.05)	6.93 (4.88, 8.98)	15.15

Abbreviations: *APOE*, apolipoprotein E; K-ROAD, Korea Registries to Overcome Dementia and Accelerate Dementia Research Project; NA-ADNI, North America Alzheimer's Disease Neuroimaging Initiative; NHW, non-Hispanic White; RMSE, root mean squared error.
[a]Average (standard deviation).
[b]Estimates (95% confidence intervals).

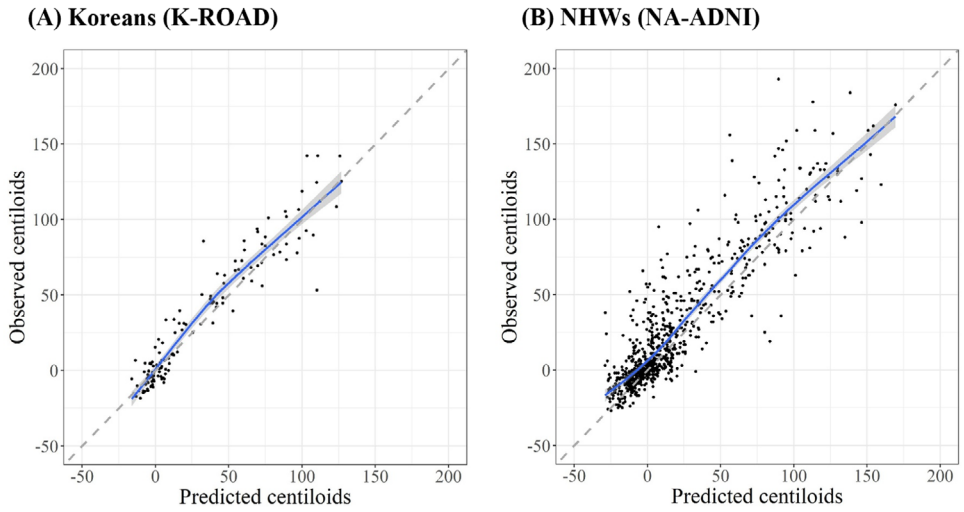

FIGURE 5 Calibration plots of Koreans and NHWs in total propensity score-matched cohort, assessing the agreement between the observed and predicted Centiloid values. The gray dashed diagonal line represents perfect calibration with an intercept of 0 and a slope of 1. The blue lines represent the calibration curves using locally estimated scatterplot smoothing (LOESS), with shaded areas indicating 95% confidence intervals. The calibration plot for Koreans (A) shows good agreement between observed and predicted Centiloid values. For NHWs (B), the calibration curve runs nearly parallel to the 45-degree reference line, indicating that the model is well calibrated; however, the smoothed curve lies slightly above the diagonal line, suggesting a systematic underestimation of Centiloid values in this group. The A4 Study was excluded as longitudinal data were unavailable. A4, Anti-Amyloid Treatment in Asymptomatic Alzheimer's Study; K-ROAD, Korea Registries to Overcome dementia and Accelerate Dementia Research Project; NA-ADNI, North American Alzheimer's Disease Neuroimaging Initiative; NHW, non-Hispanic White.

dicted CL values (Table 2). Among NHW participants from NA-ADNI, calibration slopes remained adequate (1.00, 95% CI; 0.97 to 1.03); however, the calibration-in-the-large values were > 0 (7.34, 95% CI; 6.02 to 8.66), suggesting that predicted CL values are systematically lower than observed CL values. This pattern of underestimation was consistently observed across all NHW subgroups stratified by *APOE ε*4 status and sex (Table 2). Calibration plots for graphical assessment are presented in Figure 5 and Figures 2 and 3. The RMSEs were 13.07 for Koreans and 20.25 for NHWs from NA-ADNI (Table 2), and the lower RMSE of Korean participants is consistent with the results of calibration. Validation could not be performed in NHWs from the A4 Study because longitudinal CL values were not available.

4 | DISCUSSION

This study demonstrates the application of GAMLSS-based centile curves to cross-sectional baseline data for developing age-related Aβ trajectories. Calibration with longitudinal data confirmed the robustness of this approach. Notably, lower percentiles remained relatively

stable across age, while upper percentiles exhibited marked increases, indicating progressive Aβ accumulation in CU individuals with higher baseline levels. In the comparison between ethnicities, NHWs from NA-ADNI exhibited steeper trajectories than Koreans, particularly among *APOE* ε4 carriers. An independent NHW cohort from the A4 Study showed comparable age-related Aβ patterns, supporting the generalizability and replicability of our modeling approach. Taken together, our findings emphasize the influence of ethnicity on Aβ accumulation patterns in CU populations, particularly among *APOE* ε4 carriers, and underscore the importance of population-specific strategies for early detection and intervention. Addressing ethnic variability can contribute to advancing personalized approaches to AD research and management, including both primary and secondary prevention.

In this study, we successfully developed age-related Aβ trajectories using baseline data from CU Korean participants, representing a significant methodological advancement as such trajectories were previously attainable primarily through longitudinal follow-up data, with only a few studies exploring similar approaches using cross-sectional data.[9] By validating these trajectories with our own longitudinal dataset, we demonstrated robust calibration, thereby confirming the reliability of our cross-sectional approach. A key aspect of this methodology is the application of GAMLSS, a statistical framework well suited for capturing complex, age-related changes. GAMLSS is particularly effective in handling non-normal distributions, estimating multiple parameters, and modeling non-linear patterns.[31,38] Some studies have adopted quantile regression to model growth curves of CL accumulation to capture heterogeneous accumulation patterns throughout different ages.[39,40] However, this approach has two main drawbacks: it can only analyze pre-specified quantiles and may produce unstable estimates at extreme percentiles. To address these methodological challenges, we adopted GAMLSS, which has not been applied in dementia research before. Its successful use in this study underscores its versatility and suitability for studying dynamic biomarker trajectories, such as Aβ accumulation in CU populations. This innovative approach allows efficient analysis of large, diverse populations and facilitates the identification of nuanced patterns in Aβ accumulation. The ability to infer longitudinal Aβ trajectories from baseline data not only streamlines AD research but also provides a scalable framework for examining Aβ dynamics across various populations. Consequently, our approach enables more comprehensive and inclusive studies on Aβ accumulation, thereby advancing our understanding of AD progression in CU individuals.

Using the Aβ trajectories developed from cross-sectional baseline data, we replicated the well-established effects of *APOE* ε4 on Aβ accumulation patterns, demonstrating significantly higher levels of Aβ deposition among *APOE* ε4 carriers compared to non-carriers.[12,41] This finding reinforces the role of *APOE* ε4 as a primary genetic driver of Aβ pathology in AD. While an earlier study[6] suggested *APOE* ε4 affects the initiation of Aβ accumulation but not its progression, our findings indicate *APOE* ε4 influences both the onset and accumulation rates. These differences may stem from population- or methodology-related variations; however, our use of PS matching provides a more robust approach. Another study supports our findings on *APOE* ε4's association with an earlier onset of Aβ positivity and a shorter preclinical period, although it suggests that *APOE* ε4 does not alter the rate of Aβ accumulation.[42] Additionally, it is possible that older *APOE* ε4 carriers with lower CL values are more likely to develop cognitive impairment, leading to their underrepresentation in CU cohorts at advanced ages. This may partially explain the observed decline in CL values in this subgroup. Furthermore, no significant sex differences were observed in Aβ accumulation, consistent with previous studies suggesting that sex does not substantially influence Aβ dynamics in CU populations.[43] These findings contrast with findings in cognitive trajectories, in which females often exhibit accelerated decline.[44] This discrepancy indicates that sex-specific effects may emerge later in the disease continuum, particularly as Aβ burden interacts with tau pathology and other downstream processes.[45] By validating these trajectories within our K-ROAD cohort, we demonstrate the generalizability of our approach and emphasize the central role of *APOE* ε4 in driving early Aβ accumulation.

Our analytical framework was applied to Koreans from K-ROAD and NHWs from NA-ADNI to compare age-related Aβ accumulation patterns across ethnicities. NHWs exhibited steeper trajectories than Koreans, highlighting population-specific differences in Aβ dynamics. To assess replicability, we further analyzed NHWs from the independent A4 Study cohort. The age-related Aβ accumulation patterns observed in the A4 Study were highly consistent with those from NA-ADNI, reinforcing the robustness and generalizability of our cross-sectional approach. These findings demonstrate that our method reliably captures Aβ accumulation dynamics across diverse populations.

Our major finding revealed that NHWs exhibited steeper age-related Aβ trajectories compared to Koreans, particularly among *APOE* ε4 carriers. Notably, this difference was most pronounced above the 50th percentile of the CL distribution, highlighting a greater tendency for accelerated Aβ accumulation in NHWs at higher Aβ burden levels. This pattern was consistently observed in both NA-ADNI and the independent A4 Study cohort, reinforcing the robustness of our findings across different NHW populations. These findings align with our prior observations of lower Aβ positivity in Koreans at the CU stage[21] and suggest population-specific differences in age-related Aβ trajectories. This may be partially explained by genetic factors, including a protective *SORL1* variant identified in our previous study. This variant, enriched in Asian populations but rare in Europeans, is associated with increased *SORL1* expression in microglia, which are critical for Aβ clearance.[46] Single-cell RNA sequencing further demonstrated higher *SORL1* expression in Aβ-negative compared to Aβ-positive individuals, suggesting that this variant enhances Aβ clearance by promoting SORL1 activity. The lower prevalence of this variant in NHWs may partially explain their steeper age-related Aβ trajectories. The decreasing CL values with age among Korean males, compared to NHW males, may indicate that older Korean males develop symptoms at a lower Aβ burden, underscoring population-specific Aβ dynamics. Taken together, these results emphasize the critical role of genetic and cellular mechanisms in shaping population-specific patterns of Aβ accumulation and highlight the importance of multi-ethnic studies to uncover diverse protective pathways against AD.

Our study's strength lies in its comprehensive evaluation of age-related Aβ trajectories using a robust modeling approach primarily based on baseline data, validated both internally and externally across diverse populations. Additionally, the use of PSM ensured well-balanced baseline characteristics between cohorts, enhancing the comparability and reliability of our findings. However, our study has several limitations. First, despite the use of PSM, residual heterogeneity in participant selection criteria, education levels, cognitive reserve, and PET imaging protocols may have influenced the observed Aβ accumulation patterns, even with CL scale harmonization. Second, while our model successfully derived longitudinal Aβ trajectories from baseline data, this approach may not fully capture individual variability in Aβ accumulation dynamics. Third, there are underestimations in NHWs, attributable to two key factors: large variation in CL values and a small sample size in the higher CL range within the model development set (i.e., baseline data), and long-term follow-up in the model validation set (i.e., follow-up data), particularly in NHWs from NA-ADNI. At baseline, NHW participants exhibit both substantial CL variability and small sample sizes in the higher CL range, which may limit the model's ability to fully capture higher CL values. Additionally, the NHW validation set from NA-ADNI included a significant proportion of cases (21%, 181 of 835) with follow-up durations beyond 6 years. Notably, when limiting the analysis to samples with follow-up periods under 6 years, the degree of underestimation decreased (calibration intercept reduced from 7.34 to 4.91). Furthermore, RMSE progressively increased with longer follow-up, with a marked rise beyond 6 years (Table S5 in supporting information). Despite this underestimation, our model effectively captures the differential rates of amyloid accumulation across CL values. Because our primary focus is to explore racial differences in amyloid accumulation patterns, including variations across age and accumulation rates between groups, the model's ability to capture relative trends is sufficient for addressing our research objectives. Fourth, while we speculated that population-specific genetic factors might influence ethnic differences, we did not incorporate genetic data into our models. This limits mechanistic insights, emphasizing the need for future studies integrating multi-omics data to better understand Aβ accumulation pathways. Finally, our study primarily included Korean and NHW participants, which limits the generalizability of the findings to other ethnic groups. Nevertheless, this innovative use of baseline data allows for efficient and scalable modeling of longitudinal patterns without requiring extensive follow-up, providing important insights into population-specific Aβ accumulation patterns and underscoring the need for multi-ethnic studies to refine early intervention and prevention strategies for AD.

In summary, our study developed and validated age-related Aβ trajectories in CU individuals using a cross-sectional modeling approach based on GAMLSS. Our findings revealed significant population-specific differences in Aβ accumulation between Korean and NHW cohorts, underscoring the importance of multi-ethnic research in understanding Aβ deposition dynamics. We observed differences in age-related Aβ PET trajectories between the Korean and NHW cohorts. These may reflect a combination of genetic, environmental, cultural, and health care–related factors associated with ancestry or region, rather than intrinsic racial or ethnic traits. By providing a scalable and efficient framework for modeling Aβ trajectories, our study offers valuable insights for refining population-specific strategies for AD prevention and early intervention, encompassing both primary and secondary prevention efforts.

AUTHOR CONTRIBUTIONS

Sungjoo Lee, Min Young Chun, Jun Pyo Kim, and Sang Won Seo conceptualized and designed the study and drafted the manuscript. Sungjoo Lee and Min Young Chun accessed and verified the data. Hyemin Jang, Daeun Shin, Heekyung Kang, Sohyun YIM, and Eun Hye Lee acquired the data. Sungjoo Lee and Kyunga Kim contributed to data curation and analysis. Min Young Chun, Jun Pyo Kim, and Sang Won Seo interpreted the data, with Sungjoo Lee handling statistical analysis. Funding was obtained by Sang Won Seo. The manuscript was revised by Michael Weiner and Sang Won Seo, Jun Pyo Kim, and Sang Won Seo supervised the study. All authors contributed to the final manuscript and were involved in the decision to submit for publication. Additional contributions: We thank all study participants, their families, and site investigators for their participation in the present study. Data used to prepare the present study were obtained from the ADNI study database at adni.loni.usc.edu. The investigators within the ADNI study contributed to the design and implementation of the ADNI study and/or provided data but did not participate in analysis or writing of this article.

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Alzheimer's Therapeutic Research Institute (ATRI) at the University of Southern California. The A4 and LEARN Studies were coordinated by ATRI at the University of Southern California, and the data are made available under the auspices of Alzheimer's Clinical Trial Consortium through the Global Research & Imaging Platform (GRIP). The complete A4 Study Team list is available on: https://www.actcinfo.org/a4-study-team-lists/. We would like to acknowledge the dedication of the study participants and their study partners who made the A4 and LEARN Studies possible. This research was supported by a grant of the Korea Dementia Research Project through the Korea Dementia Research Center (KDRC), funded by the Ministry of Health & Welfare and Ministry of Science and ICT, Republic of Korea (grant number: RS-2020-KH106434); a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: RS-2025-02223212); Future Medicine 20*30 Project of the Samsung Medical Center [#SMX1250081]; the "Korea National Institute of Health" research project (2024-ER1003-01); partly supported by Institute of Information & communications Technology Planning & Evaluation (IITP) grant funded by the Korea government (MSIT) (No. RS-2021-II212068, Artificial Intelligence Innovation Hub); and the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (NRF-2019R1A5A2027340).

CONFLICT OF INTEREST STATEMENT

S.E.S. has served on scientific advisory boards on biomarker testing and clinical care pathways for Eisai and Novo Nordisk and has received speaking fees for presentations on biomarker testing from Eisai, Eli Lilly, and Novo Nordisk. All other authors have no conflicts of interest to disclose. Author disclosures are available in the supporting information

CONSENT STATEMENT

Written informed consent was secured for the K-ROAD study, and the study protocol received approval from the institutional review boards of all participating centers. Furthermore, all ADNI participants provided written informed consent and underwent the protocols which were approved by the institutional review board of each participating site.

DATA AVAILABILITY STATEMENT

The anonymized data for the analyses presented in this report are available upon request from the corresponding authors.

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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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