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RESEARCH ARTICLE

Ethnic differences in the prevalence of amyloid positivity and cognitive trajectories

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Abstract

INTRODUCTION: We investigated the prevalence of amyloid beta (Aβ) positivity (+) and cognitive trajectories in Koreans and non-Hispanic Whites (NHWs).

METHODS: We included 5121 Koreans from multiple centers across South Korea and 929 NHWs from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Participants underwent Aβ positron emission tomography and were categorized into cognitively unimpaired (CU), mild cognitive impairment (MCI), and dementia stages. Age, sex, education, and *apolipoprotein E.* genotype were adjusted using multivariable logis-

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tic regression and stabilized inverse probability of treatment weights based on the propensity scores to mitigate imbalances in these variables.

RESULTS: The prevalence of Aβ+ was lower in CU Koreans than in CU NHWs (adjusted odds ratio 0.60). Aβ+ Koreans showed a faster cognitive decline than Aβ+ NHWs in the CU (B = −0.314, $p = .004$) and MCI stages (B = −0.385, $p < .001$).

DISCUSSION: Ethnic characteristics of Aβ biomarkers should be considered in research and clinical application of Aβ-targeted therapies in diverse populations.

KEYWORDS
Alzheimer's disease, amyloid-β positivity, cognitive trajectories, ethnic differences, positron emission tomography

Highlights

- Koreans have a lower prevalence of Aβ positivity compared to NHWs in the CU stage.
- The effects of Alzheimer's risk factors on Aβ positivity differ between Koreans and NHWs.
- Aβ-positive (Aβ+) Koreans show faster cognitive decline than Aβ+ NHWs in the CU and MCI stages.

1 | BACKGROUND

Alzheimer's disease (AD) is characterized by amyloid beta (Aβ) plaque accumulation with subsequent cognitive decline. Advances in Aβ positron emission tomography (PET) have enabled us to detect fibrillar Aβ deposition[1] in individuals diagnosed with cognitively unimpaired (CU), mild cognitive impairment (MCI), or dementia of the Alzheimer's type (DAT),[2,3] which refers to individuals clinically diagnosed with AD dementia. The prevalence of Aβ positivity varies according to age, sex, education, and apolipoprotein E (*APOE*) genotype.[3–7]

Recently, the emergence of novel Aβ-targeted therapies has emphasized the importance of biomarker-guided diagnosis with Aβ PET. Moreover, as new treatments become available globally, understanding the ethnicity-specific characteristics of Aβ biomarkers and cognitive trajectories is crucial in selecting the appropriate candidates and monitoring their therapeutic efficacies. However, since most studies on Aβ biomarkers' characteristics have been conducted in non-Hispanic White (NHW) populations,[1,8] knowledge regarding the prevalence of Aβ positivity and cognitive trajectories in other ethnic populations is limited.

The prevalence of Aβ positivity may differ among ethnicities. For example, several studies, mainly including CU individuals, suggested that the prevalence of Aβ positivity is lower in African Americans (AAs) than in NHWs.[9,10] In particular, considering that Alzheimer's risk factors including age, sex, education levels, and *APOE* genotypes are known to affect the development of DAT,[11–16] it is possible to hypothesize that there might be ethnic differences in the effects of these Alzheimer's risk factors on the prevalence of Aβ positivity. Alternatively, the Imaging Dementia-Evidence for Amyloid Scanning study, which included cognitively impaired individuals, did not show significant differences in the prevalence of Aβ positivity between AAs and NHWs.[17] Considering that there might be ethnic differences in cognitive decline,[18,19] these inconsistent results might be driven by the different cognitive stages of the study participants. Therefore, investigating ethnic differences in the prevalence of Aβ positivity throughout the cognitive stages in relation to Alzheimer's risk factors is crucial. This research allows for a further understanding of ethnic differences in the prevalence of Aβ positivity and cognitive trajectories, which in turn aids in the design of future prevention and treatment strategies based on ethnicity.

The aim of this study was to investigate the prevalence of Aβ positivity throughout the three cognitive stages in relation to Alzheimer's risk factors in two large multicenter cohorts of Koreans and NHWs. First, we determined whether Koreans and NHWs exhibited any difference in the prevalence of Aβ positivity throughout the three cognitive stages (CU, MCI, and DAT). Second, we determined whether the effects of Alzheimer's risk factors on the prevalence of Aβ positivity differed between Koreans and NHWs. Finally, we compared the cognitive trajectories of Aβ+ individuals between Koreans and NHWs.

2 | METHODS

2.1 | Participants

In total, 6744 participants aged 55 to 90 years were recruited from a Korean cohort obtained from the Korea Registries to Overcome and

Accelerate Dementia Research Project (K-ROAD) (Figure 1), which is a member of the worldwide Alzheimer's Disease Neuroimaging Initiative (ADNI). K-ROAD aims to develop a genotype–phenotype cohort to accelerate the development of novel diagnostic and therapeutic techniques for AD and related dementias. Overall, 25 university-affiliated hospitals in South Korea participated in the K-ROAD cohort (Figure 1A). All participants underwent neuropsychological tests, brain magnetic resonance imaging (MRI), and Aβ PET using 11C-Pittsburgh compound B (PiB), ^{18}F-florbetaben (FBB), or ^{18}F-flutemetamol (FMM). Participants were categorized into three cognitive stages: CU, MCI, and DAT. Detailed inclusion/exclusion criteria of the K-ROAD cohort are described in Supplementary Method 1.

To compare ethnic differences, we collected 929 NHW participants' data from the North American ADNI (NA-ADNI) dataset led by principal investigator Michael Weiner (Figure 1B). Detailed inclusion and exclusion criteria for the NA-ADNI data are provided on the website (http://www.adni-info.org). To achieve external validation in an independent cohort, we collected CU participants' data from the Anti-Amyloid in Asymptomatic Alzheimer's Disease (A4) study[20] and included 168 Asians and 3908 NHWs in the validation cohort (Figure 1C).

We obtained written informed consent for the K-ROAD study, and the Institutional Review Board of each participating center approved the study protocol. Additionally, the NA-ADNI Data Sharing and Publications Committee approved data use and publication.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors conducted a comprehensive review of literature using traditional sources (eg, PubMed). Our review of the literature revealed ethnic disparities in the prevalence of amyloid beta (Aβ) positivity and cognitive trajectories in Alzheimer's disease (AD), revealing a lack of studies comparing these factors between large Asian and non-Hispanic White (NHW) cohorts.
2. **Interpretation**: Our research found that the prevalence of Aβ positivity was lower in Koreans than in NHWs in the cognitively unimpaired (CU) stage. Aβ-positive (Aβ+) Koreans exhibited a faster cognitive decline compared to Aβ+ NHWs in the CU and mild cognitive impairment stages. These findings underscore ethnic differences in the characteristics of Aβ biomarkers and their association with cognitive decline.
3. **Future directions**: Ethnic characteristics of Aβ biomarkers should be considered in research on and the clinical application of Aβ-targeted therapies in diverse populations. Future studies should explore varied ethnic and diagnostic groups to optimize tailored treatment in AD.

2.2 | Amyloid PET acquisition and definition of amyloid positivity

All Korean participants underwent one of the following Aβ PET scans: PiB, FMM, or FBB. Imaging was performed according to the manufacturer's guidelines (Supplementary Method 2). We quantified Aβ burden using standardized uptake value ratios (SUVRs) from PiB, FBB, and FMM PET scans. All imaging analyses for the K-ROAD study were conducted at the laboratory of Samsung Medical Center, which served as a core center.

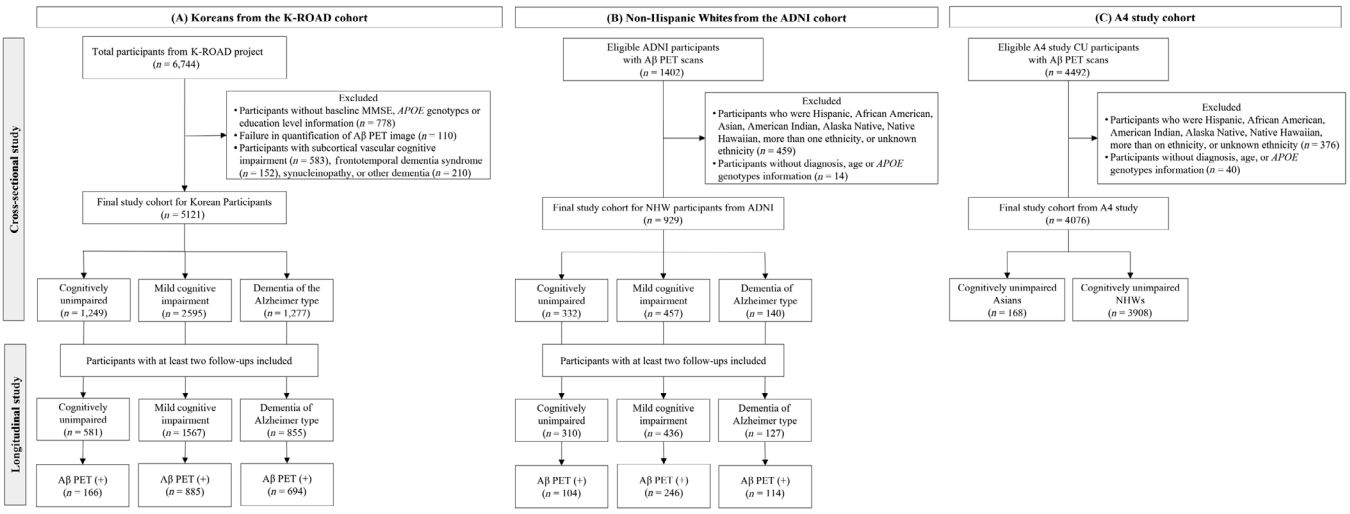

FIGURE 1 Flow diagram of study population, including (A) Koreans from K-ROAD, (B) NHWs from North American ADNI, and (C) Asians and NHWs from A4 Study cohorts. K-ROAD, Korea Registries to Overcome and Accelerate Dementia Research Project; ADNI, Alzheimer's Disease Neuroimaging Initiative; A4 study, Anti-Amyloid in Asymptomatic Alzheimer's Disease study; MMSE, Mini-Mental State Examination; APOE, apolipoprotein E; Aβ, amyloid beta; PET, positron emission tomography.

All NA-ADNI and A4 study participants underwent ^{18}F-florbetapir (AV45) PET scans, and SUVRs were obtained from their respective datasets.

To harmonize the quantitative analysis of Aβ PET across different ligands, we applied the Klunk Centiloid (CL) scale, which has been increasingly used in various cohort studies and clinical trials.[21–25] Detailed methods for obtaining SUVR and CL for the K-ROAD study are described in the Supplementary Method 2. For NA-ADNI and A4 studies, we transformed the SUVR values to CL values using a direct conversion equation ($CL = 188.22 \times SUVR_{FBP} - 189.16$), as previously established.[21,22]

For all cohorts, we defined Aβ positivity using a CL cutoff value of 20.0[26] for the study analyses.

2.3 | Longitudinal follow-up

To compare cognitive trajectories between Aβ+ Koreans and NHWs, longitudinal Mini-Mental State Examination (MMSE) scores, which were commonly administered to both cohorts, were collected from the time point of Aβ PET. Therefore, the longitudinal study included 1745 Koreans (166 CU, 885 MCI, and 694 DAT) and 464 NHWs (310 CU, 436 MCI, and 127 DAT) who underwent two or more MMSE tests and were Aβ+, with median (interquartile range [IQR]) follow-up periods of 2.2 (1.3 to 3.7) and 2.3 (1.0 to 5.0) years, respectively.

2.4 | Statistical analysis

The frequencies and proportions of participants with Aβ positivity were calculated according to diagnostic groups and ethnicity and corresponding 95% confidence interval (CI) values were estimated using the Wilson method. In the combined cohort including Koreans and NHWs, we performed multivariable logistic regression analysis to evaluate the odds of having Aβ positivity in Koreans compared with NHWs when age (continuous), sex, education (continuous), and *APOE* genotypes (three categories: ε2 carriers [ε2/ε2 and ε2/ε3], ε3 homozygotes [ε3/ε3], and ε4 carriers [ε3/ε4, ε4/ε4, and ε2/ε4]) were controlled. For validation, in the A4 study, we evaluated the odds of Aβ positivity between Asians and NHWs by fitting a multivariable logistic regression model adjusted for age, sex, education, and *APOE* genotype. To evaluate the effect of each risk factor on the odds of having Aβ positivity in Koreans and NHWs and to investigate whether the effect of each risk factor on the odds of having Aβ positivity differed between the two ethnic groups, multivariable logistic regression model was fitted including ethnicity (Koreans and NHWs), risk factors, and the interaction between ethnicity and each of the risk factors. Age, sex, education, and *APOE* genotypes were used as risk factors. In the assessment of each risk factor, the other risk factors were treated as potential confounders. In addition, when comparing the odds of having Aβ positivity and the effect of risk factors on Aβ positivity between Koreans and NHWs, to reduce for imbalance in age, sex, education, and *APOE* genotype across ethnic groups, stabilized inverse probability of treatment weights (SIPTW) based on the propensity scores was used in logistic regression model (Supplementary Method 3). To evaluate whether ethnicity affected the rate of cognitive decline, we used a linear mixed-effects model with random intercepts and random slopes of time, and adjustments were made for age, sex, education, *APOE* genotype, and baseline MMSE scores with main and interaction effects (ethnicity, time, ethnicity×time). Outliers with an absolute standardized residual >3 were excluded. All analyses were performed separately within each individual cognitive stage (CU, MCI, and DAT).

Continuous variables are expressed as median (IQR), whereas categorical variables are expressed as frequency (percentage). All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and R 4.1.3 (Vienna, Austria; http://www.R-project.org), and statistical significance was set at $p < .05$ in the two-tailed tests.

3 | RESULTS

3.1 | Characteristics of participants

Table 1 presents the demographic and clinical characteristics of the study participants. The participants comprised 5121 Koreans and 929 NHWs (1249 Koreans and 332 NHWs in the CU stage, 2595 Koreans and 457 NHWs in the MCI stage, and 1277 Koreans and 140 NHWs in the DAT stage). The proportions of *APOE* ε4 carriers among Korean and NHW participants were 24.3% and 30.1% in the CU stage ($p = .019$), 39.5% and 48.1% in the MCI stage ($p = .001$), and 47.9% and 65.0% in the DAT stage ($p < .001$), respectively, revealing the significant ethnic differences in *APOE* genotypes. Table 1 also shows the characteristics of the A4 study participants in the validation cohort.

3.2 | Prevalence of Aβ positivity in Koreans and NHWs

Figure 2 shows the prevalence of Aβ positivity in Koreans and NHWs. The Aβ positivity prevalence (%) (95% CI) in Koreans and NHWs was 20.8% (18.6% to 23.2%) and 33.7% (28.7% to 39.1%) in the CU stage, 48.6% (46.7% to 50.5%) and 56.0% (51.3% to 60.6%) in the MCI stage, and 79.6% (77.2% to 81.7%) and 87.9% (81.3% to 92.8%) in the DAT stage. In a multivariable logistic regression analysis adjusted for age, sex, education, and *APOE* genotype, the odds of Aβ positivity in Koreans compared to NHWs were lower in the CU group (adjusted odds ratio [aOR] [95% CI], 0.60 [0.43 to 0.84], $p = .003$). However, the odds of Aβ positivity did not differ between Koreans and NHWs in the MCI stage (0.83 [0.65 to 1.06], $p = .127$) and in the DAT stage (0.90 [0.50 to 1.63], $p = .733$). Similarly, in SIPTW analyses adjusted for the same covariates, the odds of Aβ positivity in Koreans compared to NHWs were lower in the CU group (aOR [95% CI], 0.57 [0.42 to 0.77], $p < .001$). However, the odds of Aβ positivity did not show significant differences between Koreans and NHWs in the MCI stage (0.82 [0.67 to 1.02], $p = .075$) and in the DAT stage (0.85 [0.50 to 1.45], $p = .561$). To validate our findings in an independent cohort, we compared the odds of Aβ positivity

TABLE 1 Demographic and clinical characteristics of study participants.

	Cross-sectional study								Longitudinal study					
	K-ROAD			ADNI			A4 study		K-ROAD			ADNI		
	Koreans (n = 5121)			NHWs (n = 929)			Asian CU (n = 168)	NHW CU (n = 3908)	Aβ+ Koreans (n = 1745)			Aβ+ NHWs (n = 464)		
	CU (n = 1249)	MCI (n = 2595)	DAT (n = 1277)	CU (n = 332)	MCI (n = 457)	DAT (n = 140)	CU (n = 168)	CU (n = 3908)	Aβ+ CU (n = 166)	Aβ+ MCI (n = 885)	Aβ+ DAT (n = 694)	Aβ+ CU (n = 104)	Aβ+ MCI (n = 246)	Aβ+ DAT (n = 114)
Age (years)	72.0 [66.0;76.0]	73.0 [67.0;78.0]	73.0 [65.0;79.0]	72.1 [67.5;76.7]	71.8 [66.4;76.9]	75.1 [70.8;79.7]	71.5 [68.2;74.6]	70.3 [67.5;74.2]	74.0 [70.0;77.0]	74.0 [68.0;78.0]	72.0 [64.0;78.0]	74.0 [69.7;78.4]	73.3 [68.3;77.9]	74.3 [70.7;79.4]
Sex (female)	821 (65.7)	1528 (58.9)	776 (60.8)	188 (56.6)	199 (43.5)	56 (40.0)	64 (38.1)	2334 (59.7)	104 (62.7)	546 (61.7)	421 (60.7)	71 (68.3)	109 (44.3)	49 (43.0)
Education (years)	12.0 [6.0;16.0]	12.0 [6.0;16.0]	12.0 [6.0;16.0]	17.0 [16.0;18.0]	16.0 [14.0;18.0]	16.0 [14.0;18.0]	16.0 [15.0;17.0]	16.0 [15.0;18.0]	12.0 [6.0;16.0]	12.0 [7.0;16.0]	12.0 [6.0;16.0]	16.0 [14.0;18.0]	16.0 [14.0;18.0]	16.0 [14.0;18.0]
APOE genotype														
ε2 carriers	127 (10.2)	188 (7.1)	73 (5.7)	38 (11.4)	32 (7.0)	5 (3.6)	15 (8.9)	412 (10.5)	7 (4.2)	27 (3.1)	22 (3.2)	7 (6.7)	2 (0.8)	1 (0.9)
ε3/ε3	818 (65.5)	1391 (53.4)	592 (46.4)	194 (58.4)	205 (44.9)	44 (31.4)	116 (69.0)	2103 (53.8)	69 (41.6)	297 (33.6)	272 (39.2)	45 (43.3)	79 (32.1)	30 (26.3)
ε4 carriers	304 (24.3)	1016 (39.5)	612 (47.9)	100 (30.1)	220 (48.1)	91 (65.0)	37 (22.0)	1393 (35.6)	90 (54.2)	561 (63.4)	400 (57.6)	52 (50.0)	165 (67.1)	83 (72.8)
MMSE	28.0 [27.0;29.0]	26.0 [23.0;28.0]	20.0 [16.0;23.0]	29.0 [29.0;30.0]	28.0 [27.0;29.0]	23.0 [21.0;25.0]	29.0 [27.0;29.0][a]	29.0 [28.0;30.0][b]	28.0 [26.0;29.0]	25.0 [23.0;27.0]	20.0 [16.0;23.0]	29.0 [28.0;30.0]	28.0 [26.0;29.0]	23.0 [21.0;25.0]

Notes: Data are presented as median (interquartile range, 25th percentile–75th percentile) for continuous variables and frequency (percentage) for categorical values.

Abbreviations: A4 study, Anti-Amyloid in Asymptomatic Alzheimer's Disease study; ADNI, Alzheimer's Disease Neuroimaging Initiative; *APOE*, apolipoprotein E; Aβ, amyloid beta; CU, cognitively unimpaired; DAT, dementia of the Alzheimer's type; K-ROAD, Korea Registries to Overcome and Accelerate Dementia Research Project; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NHW, non-Hispanic White.

[a]Values after excluding participants without baseline MMSE (n = 3) in A4 study.

[b]Values after excluding participants without baseline MMSE (n = 34) in A4 study.

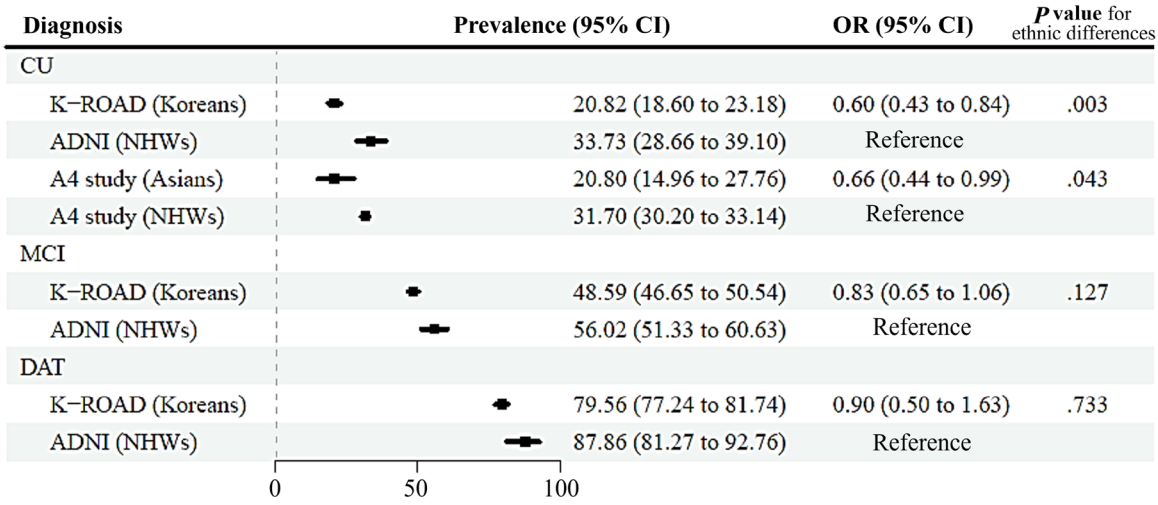

FIGURE 2 Forest plot of prevalence for Aβ positivity according to cognitive stages and ethnicity. The ORs (95% CI) of Aβ+ in Koreans compared to NHWs, adjusted for age, sex, education, and *APOE* genotype and *p* values for ethnic differences are included. The squares indicate the probability of Aβ positivity and the horizontal lines represent 95% CIs. OR, odds ratio; CI, confidence interval; CU, cognitively unimpaired; K-ROAD, Korea Registries to Overcome and Accelerate Dementia Research Project; ADNI, Alzheimer's Disease Neuroimaging Initiative; NHW, non-Hispanic White; A4 study, Anti-Amyloid in Asymptomatic Alzheimer's Disease study; MCI, mild cognitive impairment; DAT, dementia of the Alzheimer's type.

between Asians and NHWs in the A4 study consisting of CU participants, and the odds of Aβ positivity were significantly lower in Asians than in NHWs (multivariable: 0.659 [0.439 to 0.987], $p = .043$).

3.3 | Prevalence of Aβ positivity in relation to age, sex, education, and *APOE* genotypes

We examined OR for Aβ positivity according to age, sex, education, and *APOE* genotype in Koreans and NHWs (Figure 3). In the CU and MCI stages, the odds of Aβ positivity increased with age in both Koreans (CU: 1.08 [1.06 to 1.11]; MCI: 1.04 [1.03 to 1.06]) and NHWs (CU: 1.14 [1.09 to 1.20]; MCI: 1.08 [1.05 to 1.11]). In particular, Koreans in the CU stage had lower odds of Aβ positivity than NHWs as age increased (0.95 [0.90 to 0.99], $p = .0497$) (Figures 3C and S1). The analysis using SIPTW also showed the reduced odds of Aβ positivity among Koreans relative to NHWs with age in the CU stage (0.94 [0.89 to 0.99], $p = .035$). In contrast, in the DAT stage, the odds of Aβ positivity decreased with increasing age in Koreans (0.96 [0.95 to 0.98]), whereas aging did not significantly affect Aβ positivity in NHWs (0.95 [0.86 to 1.04]). Moreover, among Koreans, females had more frequent Aβ positivity compared to males in the MCI stage (1.42 [1.17 to 1.73], $p < .001$). For NHWs, females had more frequent Aβ positivity than males in the CU stage (2.39 [1.37 to 4.17], $p = .002$). Notably, in the DAT stage, Koreans exhibited higher odds of Aβ positivity with increasing educational levels (1.08 [1.05 to 1.12], $p < .001$), whereas NHWs demonstrated no significant differences in the odds of having Aβ positivity according to their educational levels. Especially in the DAT stage, Koreans had higher odds of Aβ positivity with increasing education levels compared to NHWs (1.41 [1.05 to 1.89], $p = .023$). Both Koreans (CU: 5.80 [4.04 to 8.34]; MCI: 7.78 [6.26 to 9.67]; and DAT: 6.09 [4.04 to 9.19], all $p < .001$) and NHWs (CU: 5.75 [2.95 to 11.21]; MCI: 7.09 [4.18 to 12.02]; and DAT: 16.47 [2.57 to 105.51], all $p < .001$) showed that *APOE* ε4 carriers exhibited higher odds of Aβ positivity across all cognitive stages compared to those with the ε3/ε3 genotype. In contrast, *APOE* ε2 carriers showed lower odds of Aβ positivity than those with the ε3/ε3 genotype in the MCI stage (Koreans: 0.47 [0.31 to 0.74], $p < .001$; NHWs: 0.16 [0.04 to 0.65], $p = .007$). There were no statistically significant interactions between ethnicity and *APOE* genotypes. However, effect sizes of the *APOE* genotypes were consistent across cognitive stages in Koreans but varied in NHWs, with larger effects for *APOE* ε4 carriers and smaller effects for *APOE* ε2 carriers as cognitive stages advanced. Specifically, the effects of *APOE* ε4 carriers seemed to be larger in NHWs (aOR 16.5) than in Koreans (aOR 6.1) in the DAT stage.

3.4 | Cognitive trajectories among Aβ+ participants

To investigate the ethnic differences in cognitive trajectories between Koreans and NHWs, we recruited the following Aβ+ participants: 1745 Koreans (166 CU, 885 MCI, and 694 DAT) and 464 NHWs (104 CU, 246 MCI, and 114 DAT) (Figure 1 and Table 1). Figure 4 presents mixed models showing cognitive changes according to ethnicity among Aβ+ participants in the groups. In the CU and MCI stages, the mixed models adjusted for age, sex, education, *APOE* genotype, and baseline MMSE scores indicated that Koreans showed a more rapid decline in MMSE scores over time than NHWs (CU: $B = -0.314$, $p = .004$; MCI: $B = -0.385$, $p < .001$). In contrast, in the DAT stage, there were no significant ethnic differences in the rate of MMSE score changes between Koreans and NHWs ($p = .649$).

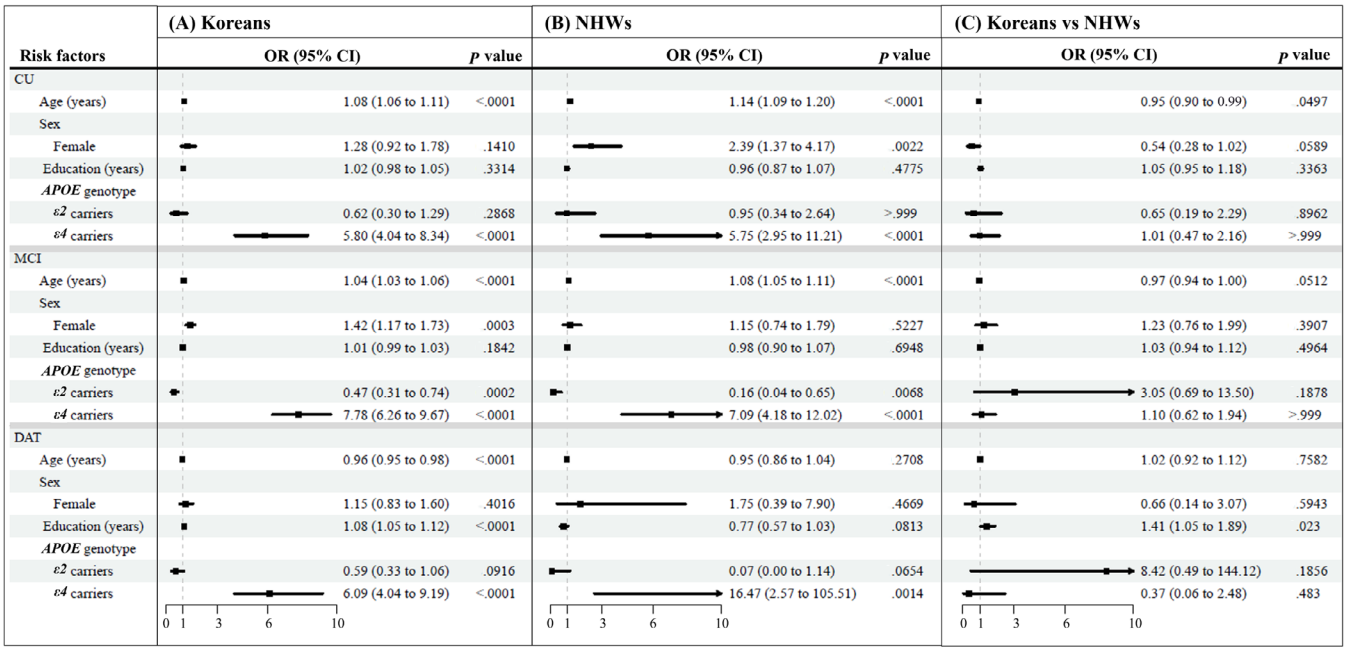

FIGURE 3 Forest plot of adjusted ORs for Aβ positivity according to age, sex, education, *APOE* genotype, and cognitive stages in (A) Koreans and (B) NHWs; and (C) adjusted ORs for Aβ positivity in Koreans compared to NHWs. (A, B) To evaluate the effect of each risk factor (age, sex, education, and *APOE* genotypes) on the odds of having Aβ+ in Koreans and NHWs and (C) to investigate whether each risk factor on Aβ+ differed between two ethnic groups, a multivariable logistic regression model was fitted including ethnicity, risk factors, and interaction between ethnicity and each of the risk factors. In the assessment of each risk factor, the other risk factors were treated as potential confounders. Squares indicate adjusted ORs for Aβ+ and horizontal lines represent 95% CI. Aβ, amyloid beta; NHW, non-Hispanic White; OR, odds ratio; CI, confidence interval; CU, cognitively unimpaired; APOE, apolipoprotein E; MCI, mild cognitive impairment; DAT, dementia of the Alzheimer's type.

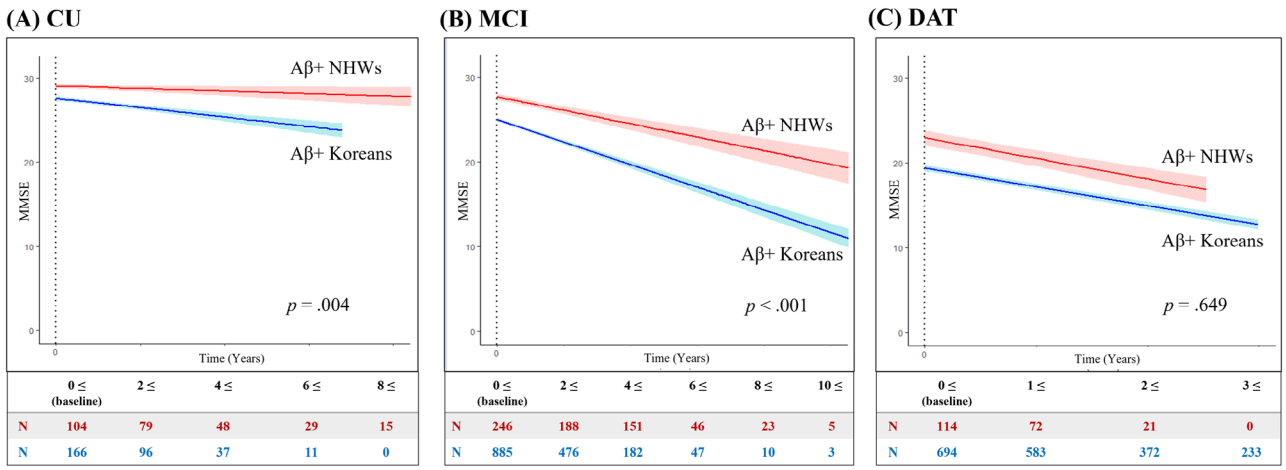

FIGURE 4 Ethnic differences in cognitive trajectories among Aβ-positive participants: (A) CU, (B) MCI, and (C) DAT stages. The red and blue solid lines and shadings indicate cognitive trajectories in Koreans and NHWs using linear mixed-effects models and 95% CIs. The number of participants during follow-up periods is shown at the bottom of the graph. Aβ, amyloid beta; NHW, non-Hispanic White; CU, cognitively unimpaired; MCI, mild cognitive impairment; DAT, dementia of the Alzheimer's type; MMSE, Mini-Mental State Examination; N, number.

4 | DISCUSSION

In this study, we examined ethnic differences in the prevalence of Aβ positivity and cognitive trajectories across three cognitive stages in relation to Alzheimer's risk factors in large multicenter cohorts of Koreans and NHWs. Our major findings are as follows. First, the prevalence of Aβ positivity was lower in Koreans compared to NHWs in the CU stage, even after accounting for Alzheimer's risk factors including age, sex, education, and *APOE* genotypes; however, this pattern was not observed in the MCI and DAT stages. SIPTW analyses also showed the same results. Second, the main effects of these Alzheimer's risk factors on Aβ positivity prevalence differed between Koreans and

NHWs. Finally, Aβ+ Koreans in the CU and MCI stages (but not the DAT stage) experienced a faster decline in cognitive trajectories than Aβ+ NHWs. Taken together, our findings suggest that the prevalence of Aβ positivity and cognitive trajectories throughout cognitive stages differ by ethnicity. These results enhance our understanding of the ethnic diversity of Aβ positivity prevalence and cognitive trajectories, underscoring their importance when considering the emergence of Aβ-targeted therapies that might be used worldwide across diverse ethnic populations.

Our first major finding was that Koreans had a lower prevalence of Aβ positivity compared to NHWs in from the CU stage; however, this pattern was not observed in the MCI and DAT stages. This may be related to the lower frequency of *APOE* ε4 carriers in Koreans than in NHWs, as the *APOE* ε4 allele is an important risk factor for Aβ positivity. However, we observed these results in the SIPTW and the multivariable analyses, with adjustments for age, sex, education, and *APOE* genotype. Our findings in the CU stage were also validated using an independent cohort from the A4 study, which recruited CU participants from across the United States, Canada, and Australia. Thus, our findings suggest that Asians have lower odds for Aβ positivity than NHWs, and this might be attributed more to ethnic differences than to geographical location. In fact, our findings are consistent with previous studies showing that the prevalence of Aβ positivity in Asians ranged from 17% to 23%, which is lower than in Europeans (approximately 30%) in the CU stage.[20,27] Moreover, the Japanese ADNI study also showed that the prevalence of Aβ positivity in the CU stage was significantly lower in Japanese participants (23%) compared to the ADNI population (44%); however, these differences were not observed in the MCI or DAT stages.[28] The histogram of Aβ PET CL values for Korean and NHW CU participants (Figure S2) might explain our findings. Specifically, Aβ PET CL values were comparable between Koreans and NHWs at the lower end of the CL histogram, but Koreans exhibited lower CL values than NHWs at the higher end. This suggests that as the Aβ burden increases, Aβ+ Koreans may experience more rapid progression from the CU stage to cognitive decline due to lower cognitive resilience compared to Aβ+ NHWs.

Our second major finding was that the main effects of these Alzheimer's risk factors on Aβ positivity prevalence differed between Koreans and NHWs. Specifically, the ethnic differences in the prevalence of Aβ positivity among CU participants were pronounced with increasing age. Given that cognitive resilience is reduced in the elderly, this finding could support our hypothesis that there may be ethnic differences in cognitive resilience to Aβ uptake. In addition, both Koreans and NHWs exhibited similar patterns of age-related increases in Aβ positivity prevalence in the CU and MCI stages, while in the DAT stage, the prevalence of Aβ positivity decreased with increasing age. Our findings were consistent with those of previous meta-analyses.[2,3,6] In particular, Aβ positivity prevalence declined more in Korean DAT participants with aging compared to NHW DAT participants. Given that the prevalence of non-AD pathologies, including TAR DNA-binding protein 43, argyrophilic grain disease, and hippocampal sclerosis increases with aging,[29] Korean DAT participants, especially the elderly, might have more non-AD pathological changes than NHW DAT participants.[30,31] Dementia patients with these non-AD pathological changes are more likely to exhibit cognitive decline, particularly memory impairment, and thus might be clinically misdiagnosed as DAT. Consequently, Koreans clinically diagnosed with DAT may include cases of dementia due to non-AD pathology, leading to a lower prevalence of Aβ positivity compared to NHWs.

Another significant finding was that, in the DAT stage, as education level increased, Koreans had higher odds of Aβ positivity compared to NHWs. Our previous studies in a Korean cohort demonstrated that lower education is related to vascular risk factors and vascular dementia,[32] while higher education was associated with Aβ positivity.[33] The ethnic differences in the effects of education might be related to the differences in the educational levels between Korean DAT participants (median 12, IQR 6 to 16 years) and NHWs (median 16, IQR 14 to 18 years).

Previous studies suggested that odd ratios of *APOE* ε4 carriers on the prevalence of Aβ positivity is lower in Asians than in NHWs.[34] However, in the present study, there was no statistical significance in the interaction between ethnicity and *APOE* ε4 alleles in each cognitive stage. Notably, while the effect sizes of the *APOE* genotypes for Aβ positivity were consistent across cognitive stages in Koreans, they varied in NHWs. In NHWs, the effects were larger for *APOE* ε4 carriers and smaller for *APOE* ε2 carriers as cognitive stages advanced.

Our final major finding was that Aβ+ Koreans in the CU and MCI (but not DAT) stages experienced a faster decline in cognitive trajectories than Aβ+ NHWs. Our findings might elucidate our first major finding showing that the prevalence of Aβ positivity was lower in Koreans in the CU stage but not in the DAT stage. That is, when Aβ burden builds up in the brain, Aβ+ Koreans might not remain in the CU stage longer and may progress to cognitive decline more rapidly than Aβ+ NHWs. This vulnerability of Aβ+ Koreans to faster disease progression could be attributed to socio-environmental and genetic factors. Specifically, elderly Koreans might have higher levels of malnutrition and stress because their childhoods were spent during the Japanese colonial period (1910 to 1945) and the Korean War (1950 to 1953).[35] Additionally, our previous study suggested that brain-derived neurotrophic factor polymorphisms (rs7481773) are correlated with Aβ uptake in Korean CU individuals, but not in NHW CU individuals.[27] Therefore, socio-environmental and genetic differences might be related to lower cognitive resilience against Aβ pathologies, leading to faster cognitive decline in Aβ+ Koreans than in Aβ+ NHWs. Alternatively, Aβ+ Koreans might have more prevalent concurrent non-AD pathologies than Aβ+ NHWs. In fact, previous studies have suggested that compared to Western individuals with AD, Asians with AD exhibit a higher prevalence of concurrent non-AD pathologies,[36,37] which is associated with a more rapid cognitive decline.[38]

The strengths of this study include its prospective setting, standardized Aβ PET and MRI protocols, and standardized genotype-phenotyping of participants across large cohorts of Koreans and NHWs. However, the study had some limitations. First, it was based on a comparison of two large multicenter studies in Korea and North America that were not harmonized. Therefore, differences in participant selection or inclusion that could not be accounted for analytically

might exist. However, this may be mitigated by advanced statistical methods (multivariable regression and SIPTW with propensity scores) controlling for the differences in age, sex, education, and *APOE* genotypes between Koreans and NHWs. Second, different Aβ PET ligands (AV45 in the ADNI study vs PiB, FMM, and FBB in the K-ROAD study) were used in the different studies; however, these three ligands are strongly correlated with each other,[39] and we used the CL method for harmonization, ensuring comparability. Third, pathological verification was lacking; therefore, we could not investigate non-AD pathological changes in the study participants. Fourth, the study lacked data regarding the socioeconomic and vascular factors and was limited to a small list of variables. Fifth, MMSE assesses memory, attention, language, and visual-spatial domains, potentially overlooking the frontal domain, but the frontal domain was also important for evaluating cognitive changes in our participants. Sixth, we validated ethnic differences in Aβ positivity only in the CU stage, due to a lack of studies that include Asians and NHWs in the MCI and DAT stages within the same cohort. Finally, our study focused on Korean participants, which might have limited the generalizability of the findings to other Asian populations. However, given that Koreans share genetic features and Confucian culture with other Asian populations, especially East Asians,[40–42] we expect that our results could be cautiously extrapolated not only to Koreans, but also to East Asians, who make up 31% of the world's population. Indeed, several smaller East Asian studies reported Aβ positivity rates for each cognitive stage that are consistent with our results.[43–45]

In conclusion, we found that Koreans had a lower prevalence of Aβ positivity than NHWs in the CU stage. Moreover, Aβ+ Koreans showed faster cognitive decline than Aβ+ NHWs in the CU and MCI stages. Therefore, our results could help clinicians understand the distinct patterns of Aβ positivity prevalence and cognitive trajectories according to ethnicity and cognitive stage and offer valuable insights to develop more personalized prevention or treatment strategies increasingly focusing on early pathologic changes in AD.

AUTHOR CONTRIBUTIONS

Hyemin Jang, Min Young Chun, Jihwan Yun, and Sang Won Seo conceptualized and designed the study and drafted the manuscript. Hyemin Jang, Min Young Chun, and Jihwan Yun accessed and verified the data. Jun Pyo Kim, Sung Hoon Kang, Hee Jin Kim, Duk L. Na, Chang-Hyung Hong, Sang Joon Son, Hyun Woong Roh, Tae-Kyeong Lee, Eek-Sung Lee, Eun Hye Lee, Daeun Shin, Yeshin Kim, and Chi-Hun Kim acquired the data. Hongki Ham and Yuna Gu contributed to data curation and analysis. Sang Won Seo and Sook-young Woo interpreted the data, with Sook-young Woo handling statistical analysis. Funding was obtained by Hyemin Jang and Sang Won Seo. The manuscript was revised by Sang Won Seo, and Michael Weiner and Sang Won Seo supervised the study. All authors contributed to the final manuscript and were involved in the decision to submit for publication.

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CONFLICT OF INTEREST STATEMENT

No authors have conflicts of interest to disclose. Author disclosures are available in the supporting information.

CONSENT STATEMENT

Written informed consent was obtained 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 STATEMENTS

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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