



Education Moderates the Biomarker–Cortical-Thickness Relationship in Females With Cognitive Decline: A Descriptive Study With Sex Comparisons

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Background and Purpose Education is a well-established proxy for cognitive reserve and hence may influence the relationship between Alzheimer's disease pathology and brain structure. This is particularly relevant in South Korea, where historical sex disparities in educational level among current elderly populations create unique cohort characteristics. This study examined how educational level moderates the biomarker–cortical-thickness relationship in females with cognitive decline, with descriptive sex comparisons used to contextualize these findings within a cohort reflecting disparities in the history of educational opportunities in South Korea.

Methods In 80 patients (58 females, 22 males) with cognitive decline, we assessed plasma amyloid- β 42 (A β 42), phosphorylated tau 181 (p-tau), and total tau levels, p-tau/A β 42 ratio, regional cortical thickness, and scores on the Mini-Mental State Examination. Given the substantial confounding between sex and educational level in this cohort, moderated mediation analyses examining the biomarker–cortical-thickness–cognition pathway were restricted to females ($n=53$ with complete data).

Results Females had a higher p-tau/A β 42 ratio ($p=0.026$) and thicker frontal cortex ($p=0.049$) despite the absence of a significant difference in age-adjusted cognition. No significant sex $\times$ educational level interaction was observed for the biomarkers or cognition. In females, educational level moderated the relationship between the p-tau/A β 42 ratio and cortical thickness ($p<0.05$ in all five brain regions), with high-educational level females showing the expected cortical thinning with pathology, while low-educational level females exhibited preserved thickness, which did not mediate the cognitive performance.

Conclusions Descriptive sex comparisons revealed a higher biomarker burden yet greater cortical thickness in females. Importantly, educational level significantly moderated the biomarker–cortical thickness relationship specifically in females, with lower-educated individuals showing structural preservation despite the presence of pathology. These findings suggest that measurements of the cortical thickness can underestimate the disease burden in lower-educated females, which highlights the need for educational level-stratified interpretations of structural biomarkers.

Keywords Alzheimer's disease; cognitive reserve; sex; education; cognitive dysfunction.

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INTRODUCTION

Alzheimer's disease (AD) and related dementias represent a growing public health challenge worldwide, including in South Korea.¹ The escalating global burden underscores the urgent need to identify modifiable and biological risk factors that influence disease onset and progression. Educational level serves as a key proxy for cognitive reserve and has been shown to influence the relationship between AD pathology and clinical outcomes. However, the mechanisms via which educational level modulates the structural brain response to pathology remain unclear.²⁻⁴ Sex has emerged as a critical biological variable in AD pathophysiology, with females comprising approximately two-thirds of diagnosed cases and often experiencing more-rapid cognitive decline, more-severe tau pathology, and diverse responses to vascular and genetic risk factors.^{5,6}

Understanding potential sex×educational level interactions is particularly relevant in South Korea, where large generational sex-related differences in educational opportunities persist in the current elderly population. If a lower educational level confers less reserve in females because they have had systematically less access, or conversely a higher educational level provides greater compensatory benefit, diagnostic cutoffs, prognostic counseling, and trial stratification may need adjustment.

Few previous studies have integrated data obtained for plasma AD biomarkers, cortical thickness, and formal interaction testing in the same cohort.^{3,6-8} The primary aim of this study was to determine how educational level moderates the relationship between plasma AD biomarkers, cortical thickness, and cognition in South Korean females with cognitive decline. We also investigated sex and educational differences in a cohort of South Korean patients with cognitive decline, focusing on clinical scores, plasma AD biomarkers, and regional cortical thickness to elucidate how these factors independently and interactively influence AD-related clinical outcomes.

METHODS

Participants

We enrolled patients presenting with memory complaints who visited the Department of Neurology and Psychiatry at Konkuk University Medical Center in South Korea from November 2021 to March 2022. Their basic demographic characteristics were assessed, including age, sex, education level, and vascular risk factors, along with the presence of hypertension (HTN), diabetes mellitus (DM), and dyslipidemia. The vascular risk score was calculated based on the presence

of HTN, DM, and/or dyslipidemia, giving a range of 0–3. Comprehensive neuropsychological tests, global cognitive assessments (Clinical Dementia Rating–Sum of Boxes [CDR-SOB] and Mini-Mental State Examination [MMSE] scores), and brain imaging were also conducted. CDR-SOB and MMSE scores were determined using standard procedures,^{9,10} and MMSE scores were converted to z-scores adjusted for age and educational level. Participants diagnosed with dementia due to nonneurodegenerative causes such as metabolic causes, trauma, tumor, psychiatric disease, or drugs were excluded, as were patients with severe hearing or vision impairments who could not undergo neuropsychological tests. Detailed exclusion criteria are provided in our previous publications.¹¹⁻¹³ Mild cognitive impairment and dementia were diagnosed based on the criteria suggested by Petersen et al.¹⁴ and the Diagnostic and Statistical Manual of Mental Disorders (5th edition),¹⁵ respectively.

No subjects refused blood tests and there were no incomplete results including outliers, and so all 80 enrolled patients (22 males, 58 females) were included in the analyses. The cohort was stratified according to sex and educational level, with those receiving 0–6 years and 7–16 years of educational level categorized in the low- and high-educational level groups, reflecting the completion of elementary school and the completion of middle and high schools, respectively. This classification reflects the historical educational system of South Korea's elderly population.

MRI data acquisition and analysis

MRI was performed at Konkuk University Medical Center using a Magnetom Skyra 3.0-Tesla unit (Siemens Medical Systems) with a 20-channel high-resolution head coil. The MRI protocol included three-dimensional (3D) T1-weighted images, 3D fluid-attenuated inversion-recovery images, and 3D susceptibility-weighted images.¹⁶ The specific parameters and protocols used for structural MRI are provided in Supplementary Table 1 (in the online-only Data Supplement). Eight of the 80 participants were excluded due to their MRI examinations being incomplete, caused either by poor image quality related to motion artifacts or by their refusal to undergo research-related MRI at our institution.

Automatic segmentation of distinct brain regions (frontal, parietal, temporal, occipital, and insular cortices) from 3D T1-weighted volumetric images was performed using the InBrain platform (<http://inbrain.com/>; MIDAS Information Technology).^{17,18} Based on the Freesurfer platform (version 6.0), InBrain applies deep-learning algorithms to the analysis of failure prediction, brain extraction, white-matter segmentation, cortex segmentation, and analytical quality management.

Plasma collection and AD biomarker analysis

Blood samples were drawn using venipuncture and collected into EDTA (ethylenediaminetetraacetic acid) tubes. Participants were required to have fasted for a minimum of 2 hours prior to sample collection. All samples were centrifuged at $2,000\times g$ for 10 min at 4°C . The plasma supernatant was collected, divided into aliquots, and then frozen at -80°C until further analysis.

The plasma levels of amyloid- β 42 ($\text{A}\beta$ 42), phosphorylated tau 181 (p-tau), and total tau were quantified using the Single Molecule Array (SIMOA) platform (Quanterix), from which the p-tau/ $\text{A}\beta$ 42 ratio was calculated.

Statistical analyses

Kolmogorov-Smirnov tests indicated that age, MMSE score, imaging biomarkers, and $\text{A}\beta$ 42 level were normally distributed. The p-tau/ $\text{A}\beta$ 42 ratio data were not normally distributed, and so were log-transformed to improve their normality for parametric testing. Continuous variables are presented as mean $\pm$ standard deviation or median and interquartile range values, while categorical variables are presented as n (%) values. Group comparisons were performed using independent t -tests (parametric), Mann-Whitney U tests (non-parametric), or chi-square or Fisher's exact tests. A generalized linear model (GLM) was used to examine sex $\times$ educational level interactions for the p-tau/ $\text{A}\beta$ 42 ratio and MMSE score, with main effects included.

To eliminate sex-educational level confounding and explore the underlying mechanisms, we restricted the sample to females ($n=53$ with complete MRI and plasma biomarker data). We conducted moderated mediation analyses using the PROCESS macro in SPSS (version 26; IBM Corp.) that was developed by Hayes and Rockwood.¹⁹ We applied PROCESS model 7, which examines a moderated mediation model in which the effect of the independent variable on the mediator is moderated by a third variable. In our model, the education level¹⁹ was specified as the moderator of the relationship between the p-tau/ $\text{A}\beta$ 42 ratio and cognition. Age was included as a covariate. PROCESS model 7 estimates conditional indirect effects by including a product term between the independent variable and the moderator, which made it possible to examine how the mediation process varied with the education level.¹⁹ The model uses ordinary least squares to estimate mediation and moderated mediation effects, as well as bootstrapping to calculate 95% confidence intervals (CIs) for the indirect effects. Specifically, bias-corrected bootstrap CIs were derived from 10,000 samples at a 95% CI; if the bootstrapped CIs do not include zero, the effect was considered significant.¹⁹

Protocol approvals, registrations, and patient consent

This prospective study was approved by the Institutional Review Board of Konkuk University Medical Center (no. KUH1170180). All procedures used in this study were performed in accordance with the ethical standards set by the Helsinki Declaration of 1975 (and as revised in 1983). Written informed consent was obtained from all participants.

RESULTS

Characteristics according to sex and educational level

The participants were aged 77.9 ± 6.9 years, 72.5% ($n=58$) were female, and they had an education level of 7.37 ± 5.25 years and an MMSE score of 18.0 ± 5.9 . There were no significant sex-related differences in age (males: 79.2 ± 6.6 years; females: 77.5 ± 7.1 years; $p=0.332$) or vascular risk factors (HTN: $p>0.999$; DM: $p=0.897$; dyslipidemia: $p=0.199$). Males were more common in the high-educational level group (males: 86.4%; females: 31.0%; $p<0.001$) and had higher MMSE scores (males: 21.2 ± 6.2 ; females: 16.8 ± 5.4 , $p=0.002$), but the MMSE z-score and CDR-SOB score did not differ significantly with sex. Regarding plasma biomarkers, the p-tau/ $\text{A}\beta$ 42 ratio was lower in males (males: -0.53 ± 0.23 ; females: -0.37 ± 0.35 ; $p=0.026$). Females showed a thicker frontal cortex (females: 4.2 ± 1.7 mm; males: 3.2 ± 2.3 mm; $p=0.049$), with near-significant differences in thickness for the parietal ($p=0.066$), temporal ($p=0.068$), occipital ($p=0.084$), and insular ($p=0.091$) cortices.

The low-educational level group included more females (low educational level: 93.0%; high educational level: 48.6%; $p<0.001$), and scored lower on the MMSE (low educational level: 15.9 ± 5.3 ; high educational level: 20.4 ± 5.8 ; $p<0.001$), but the MMSE z-score, CDR-SOB score, plasma p-tau/ $\text{A}\beta$ 42 ratio, and cortical thickness did not differ significantly between the low- and high-educational level groups. The demographic characteristics of all participants and each group are summarized in Table 1.

Interaction analyses

The GLM analyses for the p-tau/ $\text{A}\beta$ 42 ratio revealed no significant main effects of sex ($p=0.069$) or educational level ($p=0.370$), nor a significant interaction between these two variables ($p=0.820$; model $R^2=0.068$, adjusted $R^2=0.031$). Similarly, for the MMSE score neither the main effects (sex: $p=0.076$; educational level: $p=0.209$) nor the interaction term ($p=0.478$) reached statistical significance (model $R^2=0.176$, adjusted $R^2=0.144$). Formal testing of sex $\times$ educational level interactions for the regional cortical thickness was not per-

Table 1. Group comparisons according to sex and education

Variable	Males (n=22)	Females (n=58)	<i>p</i>	Low education (n=43)	High education (n=37)	<i>p</i>
Age (yr)	79.2±6.6	77.5±7.1	0.332	78.9±6.8	76.8±7.0	0.176
High education	19 (86.4)	18 (31.0)	<0.001	-	-	-
Females	-	-	-	40 (93.0)	18 (48.6)	<0.001
HTN	14 (63.6)	38 (65.5)	>0.999	29 (67.4)	23 (62.2)	0.796
DM	9 (40.9)	21 (36.2)	0.897	14 (32.6)	16 (43.2)	0.452
Dyslipidemia	4 (18.2)	21 (36.2)	0.199	14 (32.6)	11 (29.7)	0.976
MMSE score	21.2±6.2	16.8±5.4	0.002	15.9±5.3	20.4±5.8	<0.001
MMSE z-score	-0.8 [-3.0 to 0.6]	-1.4 [-2.1 to -0.5]	0.354	-1.4 [-2.0 to -0.3]	-1.1 [-2.4 to -0.2]	0.696
CDR-SOB score	4.8 [3.5 to 6.0]	5.0 [2.5 to 10.0]	0.623	6.0 [2.5 to 10.0]	4.0 [3.5 to 6.0]	0.154
Aβ42 (pg/mL)	10.0±2.9	8.8±3.9	0.228	9.5±3.7	8.8±3.6	0.429
p-tau (pg/mL)	2.8 [1.9 to 3.4]	3.4 [2.2 to 4.9]	0.185	3.2 [2.2 to 4.7]	3.1 [1.9 to 4.7]	0.710
t-tau (pg/mL)	3.3 [2.4 to 4.5]	3.0 [2.4 to 4.2]	0.872	3.1 [2.4 to 4.2]	3.2 [2.4 to 4.4]	0.717
Lg p-tau/Aβ42	-0.53±0.23	-0.37±0.35	0.026	-0.43±0.33	-0.41±0.34	0.791
Frontal thickness* (mm)	3.2±2.3	4.2±1.7	0.049	4.4±1.6	3.6±2.1	0.071
Parietal thickness* (mm)	2.9±2.0	3.7±1.5	0.066	3.8±1.4	3.1±1.8	0.078
Temporal thickness* (mm)	3.5±2.4	4.5±1.8	0.068	4.6±1.7	3.8±2.2	0.087
Occipital thickness* (mm)	2.6±1.8	3.3±1.3	0.084	3.4±1.2	2.9±1.7	0.115
Insular thickness* (mm)	3.7±2.6	4.7±1.9	0.091	4.8±1.8	4.1±2.4	0.116

Data are *n* (%), mean±SD, or median [IQR] values.

*Cortical thicknesses were only measured in the subset of participants with valid MRI data (*n*=75).

Aβ42, amyloid-β 42; CDR-SOB, Clinical Dementia Rating-Sum of Boxes; DM, diabetes mellitus; HTN, hypertension; IQR, interquartile range; Lg p-tau/Aβ42, log-transformed p-tau/Aβ42 ratio; MMSE, Mini-Mental State Examination; p-tau, phosphorylated tau 181; SD, standard deviation; t-tau, total tau.

formed due to the near-complete confounding of low educational level with female sex (since 93% of the low-educational level participants were female), which rendered the sample of low-educational level males too small for stable estimations (Supplementary Table 2 in the online-only Data Supplement).

Multiple regression analyses

The analyses of the multiple regression model aimed at identifying predictors of global cognition revealed that age ($B=-0.202$, $p=0.033$), educational level ($B=1.591$, $p=0.016$), frontal thickness ($B=-9.356$, $p=0.005$), and occipital thickness ($B=12.078$, $p=0.004$) were significantly associated with a higher MMSE score. No factor significantly predicted the cortical thickness (Supplementary Table 3 in the online-only Data Supplement).

Moderated mediation analyses in females

Moderation of the p-tau/Aβ42 ratio–cortical-thickness relationship (a-path)

Since we restricted the sample to females to eliminate sex-educational level confounding and defined cortical thickness as the mediator, age was adjusted for in these analyses based on the significant predictors identified from the mul-

tipole regression model. Educational level significantly moderated the relationship between the plasma p-tau/Aβ42 ratio and cortical thickness in all five investigated regions. The interaction effect was strongest in the occipital cortex ($b=-0.918$, standard error [SE]=0.400, $p=0.026$) and temporal cortex ($b=-0.865$, SE=0.378, $p=0.026$), followed by the frontal cortex ($b=-0.788$, SE=0.357, $p=0.032$), insular cortex ($b=-0.669$, SE=0.312, $p=0.038$), and parietal cortex ($b=-0.569$, SE=0.282, $p=0.049$) (Table 2 and Supplementary Fig. 1 in the online-only Data Supplement).

Conditional effects by education level

Decomposition of these interactions revealed distinct patterns according to educational level. In the high-educational level group, females exhibited an inverse relationship in which a higher p-tau/Aβ42 ratio was significantly associated with reduced cortical thickness. This was observed consistently in all five investigated regions, most strongly in the occipital cortex ($b=-2.612$, $p=0.028$) and temporal cortex ($b=-2.562$, $p=0.023$), followed by the frontal cortex ($b=-2.381$, $p=0.025$), insular cortex ($b=-2.351$, $p=0.005$), and parietal cortex ($b=-1.953$, $p=0.020$). Conversely, there was no significant association between biomarker burden and cortical thickness in the low-educational level group (Table 2).

Table 2. Results from moderated mediation analyses using PROCESS model 7 in females

Cortical region	Interaction coefficient (a-path) <i>b</i>	SE	<i>p</i>	Conditional effect, low-education <i>b</i> (<i>p</i>)	Conditional effect, high-education <i>b</i> (<i>p</i>)	Thickness → MMSE score (b-path) <i>b</i> (<i>p</i>)	Index of moderated mediation (95% CI from 10,000 bootstraps)
Frontal	-0.788	0.357	0.032	0.966 (0.247)	-2.381 (0.025)	-0.026 (0.932)	0.119 (-2.379 to 2.884)
Insular	-0.669	0.312	0.038	0.909 (0.215)	-2.351 (0.005)	-0.013 (0.973)	-0.155 (-2.762 to 2.512)
Temporal	-0.865	0.378	0.026	1.160 (0.190)	-2.562 (0.023)	0.033 (0.933)	-0.123 (-2.845 to 2.575)
Parietal	-0.569	0.282	0.049	0.667 (0.311)	-1.953 (0.020)	0.131 (0.806)	-0.343 (-3.098 to 2.430)
Occipital	-0.918	0.400	0.026	1.342 (0.152)	-2.612 (0.028)	-0.059 (0.874)	0.234 (-2.396 to 3.112)

Age was adjusted.

CI, confidence interval; MMSE, Mini-Mental State Examination; SE, standard error.

Mediated effects on cognition (b-path)

Despite the significant moderation of the structural path, the path from cortical thickness to the MMSE score (b-path) was not statistically significant for any region. Consequently, the index of moderated mediation was not significant for any of the five regions, since the 95% bootstrapped CIs included zero. This indicates that while educational level significantly alters how the p-tau/Aβ42 ratio is related to cortical thickness in females, this structural preservation did not translate into a statistically detectable indirect effect on MMSE scores in the analyzed model (Table 2). Direct and total effects (c-path) were also not statistically significant.

DISCUSSION

This study examined how educational level moderates the biomarker–cortical-thickness relationship in females with cognitive decline in a cohort reflecting historical educational disparities in South Korea. Descriptive sex comparisons revealed that females had higher plasma p-tau/Aβ42 ratios yet paradoxically greater cortical thickness, particularly in the frontal cortex, despite the absence of a significant difference in age-adjusted cognition. The primary mechanistic finding was that educational level significantly moderated the relationship between AD pathology and cortical structure specifically in females, revealing a dissociation pattern in lower-educated individuals wherein structural preservation coexisted with an elevated biomarker burden without conferring a cognitive benefit.

The elevated p-tau/Aβ42 ratio in females aligns with a growing body of evidence from both plasma and CSF studies demonstrating that amyloid and tau pathology is greater

in females than in males at equivalent clinical stages of cognitive impairment.^{5,20–22} This pattern has been observed across ancestries and biomarker modalities, and is thought to reflect sex-specific hormonal, genetic, or neuroinflammatory influences on the accumulation of amyloid and the spread of tau pathology.^{23,24} Notably, the absence of significant sex-related differences in Aβ42 or p-tau individually while there was a clear difference in their ratio suggests that composite plasma biomarkers could be useful for detecting sex-related effects that the use of single analytes may miss. However, this conclusion is based on the current dataset, which is characterized by a relatively modest and unbalanced sample size and so further investigations with larger, more balanced cohorts are warranted to determine whether composite biomarkers are indeed more sensitive to sex-specific pathology.

The cortical thickness was greater in females than in males, particularly in the frontal cortex, despite their higher amyloid biomarker burden. This pattern is consistent with observations made in several recent structural MRI studies involving symptomatic and preclinical cohorts.^{7,25,26} Those studies have consistently found that the cortex is thicker in females in AD-vulnerable brain regions even when the pathology load is equal or greater, a phenomenon sometimes described as transient structural compensation or delayed atrophy onset.^{3,25} Longitudinal follow-up will be critical for determining whether this apparent female advantage represents true resilience or is merely a delay before more-rapid thinning occurs once a pathological threshold is crossed, consistent with patterns documented in several large cohorts.²⁷

Educational level is a well-established proxy for cognitive reserve,²⁴ and was robustly associated with MMSE scores in the expected direction but did not interact with sex for the

p-tau/A β 42 ratio. This null interaction contrasts with some previous reports suggesting sex-related educational benefits^{3,28} but aligns with several larger studies that also failed to detect significant moderation.^{3,4} A fundamental methodological limitation of this study was the severe confounding and near collinearity between sex and educational level, which reflects the historical educational disparities in the older South Korean population. The large proportion (93.0%) of the low-educational level group being female and the relatively small sample of males ($n=22$) resulted in a significant reduction in statistical power that precluded reliable estimations of formal sex $\times$ educational level interactions. Consequently, the observed sex-related differences in biomarkers and cortical thickness must be interpreted strictly as descriptive cohort characteristics rather than definitive biological or mechanistic distinctions. This sex-educational level confounding is particularly pronounced in the South Korean elderly population, where female educational level has lagged dramatically behind that of males due to sociocultural norms.¹ To disentangle these factors in future research, it is imperative to integrate data from multiple institutions to construct larger and more-balanced cohorts that sufficiently represent the sex and educational level strata.

Despite the presence of considerable confounding, our findings demonstrate that educational level significantly moderates the relationship between the plasma p-tau/A β 42 ratio and regional cortical thickness in females. Sensitivity analyses using alternative cutoffs (0–3, 4–9, and ≥ 10 years) and a continuous variable (0–16 years) further confirmed the robustness of our results, yielding patterns consistent with the initial dichotomization at 6 years of educational level (Supplementary Tables 4 and 5 in the online-only Data Supplement). Among the females in the high-educational level group we observed a consistent and expected inverse relationship, where an increased pathological burden was significantly associated with reduced cortical thickness in all five investigated regions. In contrast, this association failed to reach statistical significance in low-educational level females. These results underscore educational level as a critical factor that modulates the structural manifestation of AD pathology, suggesting that the brain's morphological response to AD biomarkers is not uniform but instead heavily contingent upon the individual educational level.

This structural preservation pattern observed in low-educational level females likely reflects a dissociation between neurodegeneration and macrostructural cortical thinning rather than true biological resilience.^{3,8,22,23} Our observation that this preserved thickness did not translate into commensurate cognitive performance suggests that it represents a delayed morphological response to pathology rather than

cognitive reserve in the traditional sense of functional maintenance. Furthermore, this dissociation may be partially attributable to the inherent measurement limitations of the MMSE. As a global screening tool, the MMSE may lack the sensitivity required to detect subtle, domain-specific cognitive nuances that might still be supported by preserved cortical structures, especially in individuals with lower educational level.²⁹ This discrepancy further highlights the complex and potentially nonlinear relationship between structural reserve—the maintenance of physical brain integrity—and functional reserve, which is the actual capacity for cognitive performance. Several biological mechanisms may underlie this phenomenon. First, reactive astrogliosis and neuroinflammation,^{22,23} which are prominent during the early stages of AD, may induce transient glial swelling that masks early neuronal loss in MRI, particularly in individuals with a lower reserve. Second, the higher burden of vascular pathology often associated with a lower socioeconomic status can lead to chronic ischemic changes or subtle edema, which may paradoxically maintain the cortical volume despite the presence of active neurodegeneration.^{12,30,31} These factors may result in cortical thickness representing a less-sensitive biomarker of the disease burden in low-educational level cohorts. This would increase the risk of underestimating the true extent of neurodegeneration until a critical threshold is reached, after which atrophy and clinical decline may accelerate once these alternative compensatory or masking buffers are exhausted.

The strengths of the study include the multimodal integration of clinical scores, plasma AD biomarkers quantified using the ultrasensitive SIMOA, and cortical thickness measurements. However, it was also subject to some limitations. The first set of limitations include the modest sample size, the cross-sectional design, reliance on a dichotomous educational level variable, and potential for selection bias inherent when including a cohort from a single memory clinic. Second, the cognitive assessments performed in this study only employed global screening measures such as the MMSE and CDR-SOB. While these tools are widely used for clinical staging, they may lack the sensitivity to detect subtle, domain-specific cognitive changes. The absence of a comprehensive neuropsychological battery precluded more-detailed analyses of how plasma biomarkers and cortical thinning specifically relate to individual cognitive domains, such as executive function or episodic memory. The third significant limitation is the number of male participants being markedly smaller ($n=22$) than that of female participants. This imbalance prevented robust sex-stratified mechanistic analyses in males, and may have reduced the statistical power in detecting sex $\times$ educational level interactions. Furthermore, in the context of the older South Korean population, educa-

tional level often serves as a proxy not only for cognitive reserve but also for the early-life socioeconomic status,³² including the family economic conditions during childhood and adolescence, which can independently influence brain development^{33,34} and late-life neural resilience.^{33,35} Therefore, the observed effects of educational level in our study should be interpreted with caution since they may have been partially affected by broader life-course environmental advantages. While there were no significant sex-related differences in vascular risk factors, their high comorbidity may have also obscured subtler sex-related effects.

In this South Korean cohort reflecting substantial historical educational disparities, we found that educational level significantly moderated the relationship between AD biomarker burden and cortical structure in females. Lower-educated females exhibited preserved cortical thickness despite having an elevated pathological burden, but this did not confer a cognitive benefit and likely represents a delayed morphological response rather than a true reserve. This finding suggests that conventional structural measures can systematically underestimate the disease burden in lower-educated individuals, leading to the risk of delayed diagnoses. Our descriptive comparisons suggested that the females had a higher biomarker burden yet greater cortical thickness than the males; however, the small male sample and severe sex-educational level confounding preclude definitive interpretations of these sex-related observations. Critically, the absence of significant sex×educational level interactions in formal testing should not be interpreted as evidence of independent effects.

Our findings underscore the importance of educational level-stratified interpretations of structural biomarkers and highlight that the diagnostic utility of cortical thickness measurements may vary with the educational level. Future studies examining cognitive reserve and AD biomarkers in populations with cohort-specific educational disparities should employ designs that either balance sex-educational level distributions or explicitly acknowledge and address confounding in their analytical approach and interpretation. Larger studies that have an adequate statistical power are needed to definitively characterize potential sex×educational level interactions and their implications for precision-medicine approaches in AD.

Supplementary Materials

The online-only Data Supplement is available with this article at <https://doi.org/10.3988/jcn.2025.0686>.

Availability of Data and Material

The datasets analyzed in this study are available from the corresponding author upon reasonable request.

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Conflicts of Interest

Seung Hyun Kim, a contributing editor of the *Journal of Clinical Neurology*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

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