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RESEARCH ARTICLE

Polygenic risk score of Alzheimer's disease is associated with cognitive trajectories and phenotypes of cerebral organoids

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Abstract

INTRODUCTION: Polygenic risk score (PRS) identifies individuals at high genetic risk for Alzheimer's disease (AD), but its utility in predicting cognitive trajectories and AD pathologies remains unclear. We optimized PRS (optPRS) for AD, investigated its association with cognitive trajectories and AD phenotypes of cerebral organoids.

METHODS: Using genome-wide association study (GWAS) summary statistics from a European population, we developed optPRS to predict AD in Korean individuals (n = 1634). We analyzed the association between optPRS and cognitive trajectories

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(n = 771). We generated induced pluripotent stem cell–derived cerebral organoids from patients with high (n = 3) and low (n = 4) optPRS to evaluate amyloid beta (Aβ) and phosphorylated tau (p-tau) levels.

RESULTS: OptPRS predicted AD dementia and Aβ positivity, independent of apolipoprotein E (*APOE*). Higher optPRSs correlated with rapid cognitive decline. Cerebral organoids from the high optPRS group exhibited increased Aβ insolubility and p-tau levels.

CONCLUSION: OptPRS predicted cognitive decline and AD phenotypes of cerebral organoids, supporting its use in risk assessments and drug-screening platform.

KEYWORDS
Alzheimer's disease, amyloid beta, cognitive trajectory, organoids, phosphorylated tau, polygenic risk score

Highlights

- Optimized polygenic risk scores (optPRSs) improve the prediction of Alzheimer's disease (AD) dementia and amyloid beta positivity (Aβ+).
- High optPRS is associated with faster cognitive decline, particularly in Aβ+.
- Induced pluripotent stem cell (iPSC)–derived cerebral organoids from high optPRSs show high Aβ insolubility and phosphorylated tau (p-tau).
- PRS genetic risk stratification provides insight into AD progression and pathology.

1 | INTRODUCTION

Alzheimer's disease (AD), the most common neurodegenerative disorder, is influenced by multiple genetic factors, in addition to the well-known apolipoprotein E (*APOE*) gene. Polygenic risk scores (PRSs) aggregate the effects of multiple single-nucleotide polymorphisms (SNPs) identified through genome-wide association studies (GWASs). They have emerged as valuable tools to distinguish individuals at high versus low genetic risk for AD.[1] Despite their potential, the clinical utility of PRSs remains limited by their lack of generalizability across diverse populations. Recent genetic studies, including those informing PRS construction, have focused primarily on populations of European ancestry, raising questions about the applicability of PRSs to non-European populations, particularly Asians.[2] Our previous work addressed this limitation by evaluating the transferability of AD PRSs across Western and East Asian populations, confirming their utility in an Asian context.[3] Previous evaluations of AD PRSs utilized 39 SNPs; developing an updated PRS with improved robustness is essential to enhance further analysis.

Although numerous studies on AD PRSs exist,[4,5] relatively few have included amyloid beta (Aβ) biomarkers to investigate their association with cognitive trajectories in AD.[6] Previous studies have shown that PRSs beyond the *APOE* gene can predict AD or the conversion of mild cognitive impairment (MCI) to AD dementia (ADD),[1,7,8] but these studies lacked Aβ biomarkers. Another study showed the utility of AD PRSs in identifying MCI; however, this finding was limited to participants in their 50s.[9] Other studies have demonstrated that higher AD PRSs are associated with more pronounced abnormalities in cortical thickness and hippocampal volume.[10–12] A recent study has explored the association of PRSs with cognitive decline in Aβ-positive cognitively unimpaired (CU) individuals,[13] but the association was no longer evident when *APOE* was excluded from the PRS. Whether PRSs influence longitudinal cognitive trajectories in AD, particularly in relation to Aβ deposition, remains unexplored.

True genetic susceptibility to AD, as determined by PRS, can be validated effectively using induced pluripotent stem cell (iPSC)–derived cerebral organoid models. This approach is highly effective for identifying genetic effects as it excludes the influence of environmental factors experienced by each patient throughout life. The iPSCs derived from fibroblasts or peripheral blood mononuclear cells (PBMCs) of patients with AD, can be differentiated into neurons or glial cells that exhibit AD-related pathologies.[14–16] Cerebral organoids, consisting of various brain cell types, allows the formation of extracellular Aβ aggregates and subsequent tauopathy, such as tau hyperphosphorylation, thereby more effectively recapitulating AD progression.[17] The validity of cerebral organoid models has been confirmed through comparisons with pathological features observed in donor brains, underscoring their potential utility in AD study.[16] Although numerous studies have investigated the role of single genetic factor such as *APOE* in AD using organoid models,[18–20] no studies have yet explored the role of PRS. Moreover, important questions remain regarding the specific phenotypes that are most representative of disease progression.

In this study, we first optimized the PRS by modifying the SNP components of previously developed PRSs to develop a more accurate PRS

combination, which was subsequently validated for its performance in predicting ADD and Aβ positivity. Second, we investigated the association between the optimized PRS and cognitive trajectories, assessing whether this association differs based on Aβ-positive status. Finally, we analyzed Aβ and tau expression levels in cerebral organoids derived from iPSCs of representative individuals from high- and low-risk PRS groups. By integrating genetic risk stratification with advanced cellular models, this study aims to provide a deeper insight into the clinical utility of PRSs in AD, potentially providing personalized risk assessment and targeted intervention strategies.

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed the literature using PubMed and prior genome-wide association studies on Alzheimer's disease (AD) polygenic risk scores (PRSs). Previous studies focused mainly on European populations and lacked amyloid beta (Aβ) biomarker validation. Few explored PRS effects on cognitive decline or AD pathology. Investigating PRS-dependent AD phenotypes using induced pluripotent stem cell (iPSC)–derived organoids remains unclear.
2. **Interpretation**: Our optimized PRS (optPRS) improved its predictive performance for AD dementia and Aβ positivity. High optPRS is associated with faster cognitive decline, particularly in Aβ+ individuals. iPSC-derived cerebral organoids from high optPRS individuals show increased Aβ insolubility and tau hyperphosphorylation compared to low optPRS individuals, providing biological validation of optPRS relevance in AD pathology.
3. **Future directions**: Future studies should refine PRS models in multi-ethnic populations and validate their effects with expanded biomarker assessments. Further research using cerebral organoid models is needed to explore PRS-driven AD mechanisms and potential personalized therapeutic targets.

2 | METHODS

2.1 | Study participants

This study recruited 1634 participants who visited the memory clinics of 25 centers in South Korea between January 2013 and July 2019. Of these, 1255 participants were recruited from the Samsung Medical Center, 202 participants were recruited from a multi-center study of the KBASE (Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's Disease),[21] and 99 participants were drawn from a multi-center clinical research platform study based on the dementia cohort, collectively forming Dataset 1 for validation. In addition, 379 participants were recruited from the Biobank Innovation for chronic Cerebrovascular disease with ALZheimer's disease Study (BICWALZS),[22] which constituted Dataset 2 for replication analysis.

All participants underwent neuropsychological tests,[23] brain magnetic resonance imaging (MRI), and Aβ positron emission tomography (PET) (^{18}F-florbetaben [FBB] or ^{18}F-flutemetamol [FMM]) scans.[24] The details regarding Aβ PET acquisition and analysis are provided in the Supplementary Material. The syndromal staging of the cognitive continuum included CU, amnestic MCI (aMCI), and ADD.

Among the 1225 participants, 771 completed a minimum of two follow-up neuropsychological tests, including the Korean-Mini-Mental State Examination (K-MMSE)[25] and Clinical Dementia Rating–Sum of Boxes (CDR-SB) within the 3-year period before and after baseline Aβ PET. Thus 771 participants were included in the longitudinal cognitive trajectory analysis.

To further evaluate the generalizability of PRS in East Asian populations, an independent cohort of Chinese individuals from the UK Biobank[26] under application number 33002 was included as Dataset 3. Among 1741 available samples, genetic data passing quality control (QC) were available for 1442 individuals, of whom 15 were diagnosed with ADD. Detailed information is provided in the Supplementary Material.

2.2 | Genotyping and imputation

The DNA samples were genotyped using an Illumina Asian Screening Array BeadChip (ASA Chip, Illumina, CA, USA) (n = 1509). A subset of the samples (n = 125) was genotyped using an Affymetrix customized Korea Biobank Array chip (Affymetrix, CA, USA).[27]

QC for SNP data was conducted using PLINK Version 2.0 software[28] and imputation was conducted using Minimac4 software[29] at the University of Michigan Imputation Server. The QC and imputation process were performed according to the methods reported in our previous work.[3]

To assess and control for population stratification, we conducted principal component analysis (PCA) on genome-wide SNP data using EIGENSOFT.[30] For ancestry inference and validation, we merged the genotype data of our study with reference genotype data from the 1000 Genomes Project after matching SNPs and performing QC to retain common, high-quality variants. PCA was conducted on the reference panel, and then our cohort samples were projected into the principal component (PC) space defined by the 1000 Genomes Project. The first four PCs from this analysis, which capture the major axes of genetic variation and minimize confounding due to population structure, were included as covariates in all association analyses.

For the UK Biobank cohort (Dataset 3), genotyping was performed using either the Affymetrix UK BiLEVE Axiom array or the Affymetrix UK Biobank Axiom array (UKBB Version 3; March 2018), covering more than 800,000 SNPs. After QC and imputation, 1442 Chinese

individuals with high-quality genetic data were included in the present analyses. Detailed QC and imputation procedures for the UK Biobank samples are described in the Supplementary Material.

2.3 | PRS construction

Summary statistics were generated from the European International Genomics of Alzheimer's Project (IGAP) GWAS (11,480,632 SNPs from 21,982 AD cases and 41,944 controls)[31] to construct a PRS for the Korean population. Based on previous data,[1,5,32] we excluded 3877 SNPs surrounding *APOE* (chromosome 19, 44,400–46,500 kb, GRCh37/hg19) to ensure that the PRS was independent of the *APOE* region. PRS generation was performed using PRSice-2,[33] with IGAP GWAS summary statistics serving as the derivation dataset. To derive a predictive model, we evaluated the inclusion of SNPs across a range of *p*-value thresholds (ranging from 5×10^{-8} to 1.0) and linkage disequilibrium-based clumping r^2 values (0.1–0.9 within 1000 kb) using data from Dataset 1 (n = 1255 Korean individuals). Logistic regression models were applied to identify the combination of thresholds that maximized Nagelkerke's r^2 value, which is a measure of the variance explained by the model.

Through the process described, 39 SNPs were initially selected in a previous study (defined as PRS39).[3] To ensure the consistency and robustness in our Korean cohort, we further excluded eight SNPs whose effect directions (β) were opposite of those in the IGAP reference, resulting in a final set of 31 SNPs. Using this refined 31 SNP set, we generated an optimized PRS, referred to as optPRS. Individual optPRSs were computed as the weighted sum of the risk alleles using the β coefficients from the IGAP GWAS via PLINK.[28] For each individual, the optPRS was calculated as the sum of the number of effect alleles at each SNP, weighted by its corresponding β coefficient:

$$optPRS_i = \sum_{j=1}^{31} \beta_j \times genotype_{ij}$$

where $genotype_{ij}$ represents the number of effect alleles (0, 1, or 2) for SNP_j in $individual_i$. The final optPRS was standardized (z-score) prior to association analyses.

For group-based analyses, the optPRS was categorized into quartiles based on its distribution: first quartile (0–25th percentile, lowest optPRS values), second quartile (25th to 50th percentile), third quartile (50th to 75th percentile), and fourth quartile (75th to 100th percentile, highest optPRS values). In iPSC-derived cerebral organoid experiments, participants were further grouped into low optPRS (first and second quartiles) and high optPRS (third and fourth quartiles) groups. The same protocol was applied to independent replication cohorts (Datasets 2 and 3) to validate the predictive performance of the optPRS. Details of the SNP selection and effect sizes are provided in Table S1.

2.4 | Validation and replication of the optPRS for AD

After calculating each participant's optPRS, we performed a logistic regression analysis to determine whether the optPRS derived from the summary statistics for the ADD risk based on European populations was associated with ADD in the study after adjusting for age, sex, education year, *APOE* ε4 carrier status, and the first four PCs of genetic ancestry. To verify whether the association of the optPRS with ADD varied with the *APOE* ε4 carrier status, we performed the same analysis after stratifying the participants into *APOE* ε4 carriers and non-carriers in the Dataset 1. In addition, we replicated the analysis using the replication sets (Datasets 2 and 3) to confirm the association between optPRS and ADD, adjusting for the same covariates.

2.5 | Generation of iPSCs

We selected four participants from the low optPRS group and three from the high optPRS group. The iPSC lines were generated from the PBMCs of each participant, which were transduced with reprogramming factors using the CytoTune-iPS 2.0 Sendai Reprogramming kit (Thermo Fisher, #A16518),[34] following the manufacturer's protocol (Figure S1). The cells were cultured in mTESR1 medium (Stemcell Technologies, #ST85850) on iMatrix 511 silk (Nippi, #892-021) coated plates.[35] For passaging, 2 mM ethylenediaminetetraacetic acid (EDTA) was used, and Y27632 (Selleckchem, #S1049)[36] was added to the medium within 24 h.

2.6 | Generation and characterization of cerebral organoids

The iPSCs were dissociated and collected by centrifugation at 160 × *g* for 5 min. The iPSCs were then seeded at a density of 0.9×10^4 cells/well into V-shaped 96-well plates (Corning) pre-coated with 1% Pluronic acid (Sigma-Aldrich). The cells were cultured in the appropriate media to generate cerebral organoids as described previously,[15] and maintained until Day 60, when they were sampled for immunohistochemistry, immunoblotting, or enzyme-linked immunosorbent assay (ELISA). This time point was selected based on previous research that observed increased Aβ accumulation in AD cerebral organoid models—such as those carrying the Swedish K670N/M671L double mutation of the Amyloid Precursor Protein (APP) gene, known as APPswe—after 60 days of culture compared to controls.[17] At this 60-day stage, excitatory neurons are present, with neural progenitor cells remaining active. Conversely, glial cells, including astrocytes, are rarely observed, as they are typically expected to become more prevalent from around 3 months of culture.[15,37] Detailed protocols are provided in the Supplementary Material. Details of key reagents and resources used in this study are provided in Table S2. The 60-day time point was

selected based on previous findings that cerebral organoids derived from the iPSCs of patients with autosomal dominant AD mutations show Aβ accumulation after 2 months of culture,[17] whereas iPSCs from late-onset patients with AD exhibit these phenotypes slightly later, possibly due to increased glial populations.[15] Given our hypothesis that a high optPRS accelerates AD pathology, we analyzed 2-month-old organoids.

2.7 | Statistical analysis

Categorical variables were compared using the chi-square test (χ^2) test and are presented as frequencies (percentages). Continuous variables were analyzed using Student's *t*-test and are presented as means ± SD.

Linear mixed-effects models were used to investigate the effects of optPRS on the time-varying K-MMSE and CDR-SB scores. We included fixed effects as follows: age, sex, *APOE* ε4 carrier, cognitive status (categorized as CU, aMCI, or ADD), time interval (*t*) between baseline and each follow-up time point, two-way interaction terms of optPRS and time interval (*t*). The patients were included as random effects. In addition, we performed a subgroup analysis by dividing the participants into Aβ+ and Aβ− groups, as well as stratified analyses within each cognitive status group (CU, aMCI, and ADD).

Statistical significance was set at a p-value < 0.05 in two-tailed tests. All statistical analyses and result visualizations were performed using R Version 3.6.1 (R Project for Statistical Computing).

Organoid images were analyzed using the ImageJ software (National Institutes of Health). A 200 × 200 μm^2 area on the surface of each organoid was selected for analysis. Signal quantification was performed by multiplying the mean intensity value of each signal by the corresponding area to obtain the total signal. Aβ particle analysis was conducted using the Analyze Particles plugin in ImageJ, with particles larger than 0.1 μm^2 counted to determine the total number of particles in the specified region. Western blotting and ELISA results from the low optPRS and high optPRS organoids were compared using an unpaired *t*-test. In addition, Pearson's correlation coefficient was estimated to examine the correlation between the insoluble-to-soluble Aβ42 ratio and p-tau181 levels. Data were analyzed using GraphPad Prism Version 10.1.2.

3 | RESULTS

3.1 | Participants

Dataset 1 included 1255 participants with a mean (SD) age of 72.2 (8.9) years (739 women, 58.9%). Dataset 2 included 379 participants with a mean (SD) age of 69.8 (9.3) years (230 women, 60.7%). PCA with data from the 1000 Genomes Project revealed an ethnic overlap of our dataset with those of other East Asian populations (Figure S2). Among these participants, longitudinal follow-up data were available for 771 participants who completed at least two neuropsychological assessments within a 3-year period before and after the baseline Aβ PET scan. This subgroup had a mean (SD) age of 70.5 (8.5) years, with 59.1% women.

Detailed clinical characteristics stratified by genetic risk group (optPRS quartile groups) of the participants are shown in Table 1. There was no statistically significant difference in age, sex, years of education, prevalence of *APOE* ε4 carrier, baseline K-MMSE scores, and baseline CDR-SB scores.

TABLE 1 Baseline characteristics of participants.

	optPRS*				
	Low optPRS group		High optPRS group		
	1st quartile (n = 187)	2nd quartile (n = 193)	3rd quartile (n = 195)	4th quartile (n = 196)	p-value
Age, mean ± SD, y	70.9 ± 8.5	70.5 ± 8.5	70.2 ± 8.6	70.2 ± 8.3	0.873
Women, *n* (%)	101 (54.0%)	108 (56.0%)	127 (65.1%)	120 (61.2%)	0.107
Education, mean ± SD, y	10.8 ± 4.9	11.2 ± 5.0	10.6 ± 5.1	11.3 ± 4.9	0.478
APOE ε4 carrier, *n* (%)	71 (38.4%)	86 (44.6%)	94 (48.5%)	90 (46.2%)	0.236
Aβ PET positivity, *n* (%)	94 (50.3%)	118 (61.1%)	118 (60.5%)	124 (63.3%)	0.048
Diagnosis, *n* (%)					0.027
CU	77 (41.2%)	64 (33.2%)	65 (33.3%)	51 (26.0%)	
aMCI	35 (18.7%)	39 (20.2%)	28 (14.4%)	45 (23.0%)	
ADD	75 (40.1%)	90 (46.6%)	102 (52.3%)	100 (51.0%)	
Baseline K-MMSE, mean ± SD	24.8 ± 4.9	24.3 ± 5.0	24.0 ± 5.0	24.0 ± 4.8	0.357
Baseline CDR-SB, mean ± SD	2.18 ± 2.53	2.42 ± 2.80	2.61 ± 2.88	2.38 ± 2.27	0.483

Abbreviations: Aβ, amyloid-beta; ADD, Alzheimer's disease dementia; aMCI, amnestic mild cognitive impairment; *APOE*, apolipoprotein E; CDR-SB, Clinical Dementia Rating Sum of Boxes; CU, cognitively unimpaired; K-MMSE, Korean version of the Mini-Mental State Examination; optPRS, optimized polygenic risk score; PET, positron emission tomography; SD, standard deviation.

*Participants were stratified into quartile groups based on the optPRS distribution (0-25th, 25-50th, 50-75th, and 75-100th percentiles).

3.2 | Generation of optPRS and replication

To determine the most predictive parameters for PRS generation, we applied PRSice-2 using summary statistics from the IGAP GWAS. For the PRS39, the highest Nagelkerke R^2 value (0.020) was observed when the *p*-value threshold and linkage disequilibrium clumping value were set at 4.15×10^{-6} and 0.1, respectively. To enhance robustness, we excluded eight SNPs with opposite effect directions (β) relative to the IGAP reference (Table S1 and Figure S3), generating optPRS, which achieved a higher Nagelkerke r^2 value of 0.023.

In the Dataset 1, the optPRS was significantly associated with an increased risk of ADD, with an odds ratio (OR) per SD increase of 2.44 (95% confidence interval [CI]: 1.65–3.62, $p = 8.30 \times 10^{-6}$), whereas PRS39 showed an OR per SD increase of 1.95 (95% CI: 1.40–2.72, $p = 2.27 \times 10^{-5}$). A similar pattern was observed for Aβ deposition: OR per SD increase was 2.05 (95% CI: 1.37–3.09, $p = 5.07 \times 10^{-5}$) for optPRS, whereas it was 1.81 (95% CI: 1.32–2.48, $p = 2.23 \times 10^{-4}$) for PRS39. The Nagelkerke's r^2 and OR values were derived from logistic regression models adjusted for age, sex, education year, *APOE* ε4 carrier status, and the first four PCs of genetic ancestry. Replication analysis in Dataset 2 confirmed the association between optPRS and ADD (OR per SD increase = 2.08, 95% CI: 1.19–3.67, $p = 0.011$), again outperforming PRS39 (OR per SD increase = 1.85, 95% CI: 1.05–3.32, $p = 0.040$). For Aβ deposition in Dataset 2, the OR per SD increase was 1.92 (95% CI: 1.12–3.34, $p = 0.004$) for optPRS, whereas it was 1.89 (95% CI: 1.11–3.28, $p = 0.021$) for PRS39. To further assess generalizability, we analyzed the UK Biobank Chinese cohort (Dataset 3), where optPRS remained significantly associated with ADD (OR per SD increase = 1.97, 95% CI: 1.17–3.32, $p = 0.011$), outperforming PRS39 (OR per SD increase = 1.73, 95% CI: 1.03–2.91, $p = 0.038$), (Table S3).

We further examined the joint effects of optPRS quartiles and *APOE* ε4 carrier status on ADD and Aβ deposition. We observed a stepwise increase in the risk of ADD and Aβ deposition according to the optPRS quartiles in both *APOE* ε4 carriers and non-carriers (Figure 1). Notably, compared with *APOE* ε4 non-carriers in the first optPRS group, the *APOE* ε4 carriers in the fourth optPRS group showed a 7.37-fold (95% CI: 4.30–13.16) increased risk for ADD and a 16.26-fold (95% CI: 9.08–30.76) increased risk for Aβ positivity.

3.3 | Effects of optPRS on cognitive trajectories

In the longitudinal analysis, participants in the higher optPRS quartile showed more rapid cognitive decline and faster progression of disease severity, as measured by the K-MMSE (*p* for trend = 0.005) and CDR-SB scores (*p* for trend = 0.002), respectively (Figure 2 and Table S4).

In the longitudinal analysis, participants in the fourth optPRS quartile showed more rapid cognitive decline and faster progression of disease severity compared to those in the first optPRS quartile, as measured by the K-MMSE ($p = 0.004$) and CDR-SB scores ($p = 0.004$), respectively. Moreover, higher optPRS quartile or higher score of optPRS was associated with more rapid cognitive decline and faster progression of disease severity as measured by the K-MMSE (*p for trend* = 0.005; $p < 0.001$) and CDR-SB scores (*p for trend* = 0.002; $p < 0.001$), respectively (Figure 2 and Table S4).

In addition, we found that this association was more prominent in Aβ+ individuals. There was no significant effect of the optPRS on the rate of cognitive decline or disease severity in the Aβ− group. However, in the Aβ+ group, participants in the fourth optPRS quartile showed more rapid cognitive decline and faster progression of disease severity, as measured by K-MMSE ($p = 0.009$) and CDR-SB scores (*p* for trend = 0.016), respectively. In the Aβ+ group, higher optPRS quartile or higher score of optPRS was associated with more rapid cognitive decline and faster progression of disease severity as measured by the K-MMSE (*p* for trend = 0.016; $p = 0.003$) and CDR-SB scores (*p* for trend = 0.009; $p = 0.003$), respectively (Figure 2 and Table S4).

When stratified analyses by cognitive status (CU, aMCI, and ADD), aMCI patients with higher score of optPRS showed faster progression of disease severity as measured by CDR-SB ($p = 0.038$), (Table S5).

3.4 | iPSC derivation and cerebral organoid generation

To generate iPSCs, we selected four individuals from the low optPRS group (first and second quartiles) and three from the high optPRS group (third and fourth quartiles), (Figure 3A). PBMC donors in the high optPRS group exhibited a more rapid cognitive decline in MMSE scores than those in the low optPRS group ($p = 0.003$) (Figure 3B). We confirmed normal chromosomal normality and pluripotency of all iPSC lines generated (Figure S4). As rejuvenation during iPSC generation minimizes the involvement of aging and environmental factors while maximizing the genetic contributions of PRS, this strategy can represent PRS-dependent AD development. The iPSC lines were produced at the Samsung Medical Center and transferred to the Daegu Gyeongbuk Institute of Science and Technology, with the optPRS group information blinded until the end of the experiments and analysis.

From these iPSCs, cerebral organoids were developed to investigate PRS-dependent differences in AD-related phenotypes. During the creation of cerebral organoids, all lines from the high optPRS group (#3, #4, and #6) produced very small or no cerebral organoids in the first and second batches (Figure 3C, D). In the third differentiation batch, we successfully generated analyzable cerebral organoids from all lines used for further analyses (Figure 3D). However, #6 from the high optPRS group continued to show persistently poor organoid formation, resulting in insufficient samples for downstream biochemical analyses and subsequent exclusion from further analyses.

3.5 | Analysis of AD-related pathological phenotypes in cerebral organoid models

Immunostaining of cerebral organoids for Aβ revealed a tendency for larger particles to be more prevalent in high optPRS group compared to low optPRS group (Figure 4A, B). Immunoblotting performed on cerebral organoids at the same time point also showed no differences in

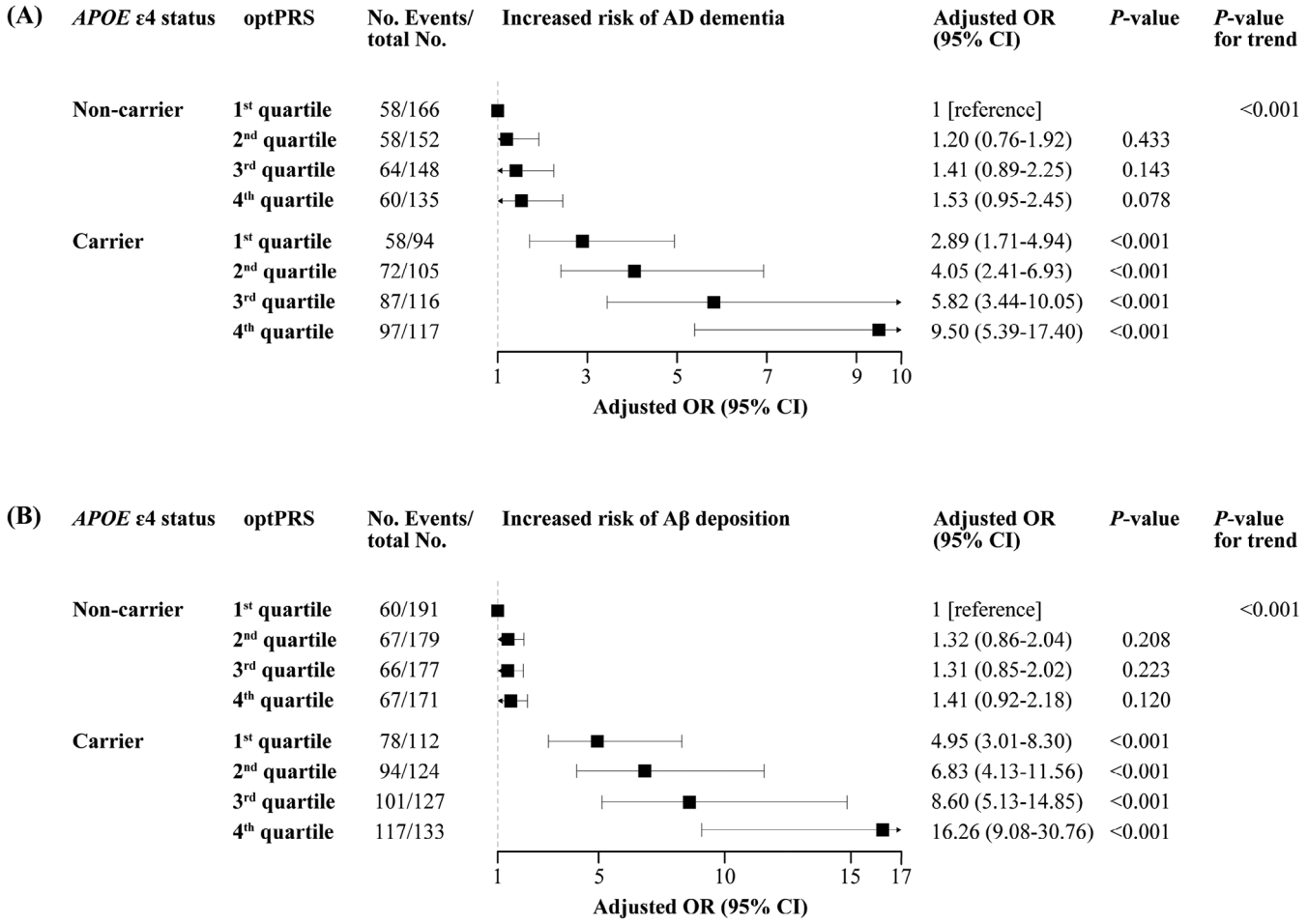


FIGURE 1 Forest plots of Alzheimer's disease dementia–related outcomes according to optPRS quartiles and *APOE* ε4 status. (A) Risk of Alzheimer's disease dementia across optPRS quartiles, stratified by *APOE* ε4 carrier status, using the first quartile as the reference group. (B) Risk of Aβ deposition in the same stratified groups, also using the first quartile as reference. Adjusted odds ratios (95% CIs) are presented for each group. Aβ, amyloid beta; *APOE*, apolipoprotein E; CI, confidence interval; optPRS, optimized polygenic risk score.

Aβ expression. However, tau hyperphosphorylation (pT217 and pS396) was significantly increased in the high optPRS group (Figure 4C, D).

As we observed an increase in Aβ aggregates in the immunofluorescence images of high optPRS group (Figure 4A) but no difference in Aβ levels in the lysed portion using Radioimmunoprecipitation assay (RIPA) buffer (Figure 4D), we separately measured RIPA-soluble and insoluble Aβ by ELISA. However, in the high optPRS group, soluble Aβ42 was significantly decreased ($p = 0.020$), but insoluble Aβ42 levels did not differ compared to the low optPRS group, indicating an increase in the insoluble fraction of Aβ42 in the high optPRS group (Figure 4E). The insoluble-to-soluble Aβ42 ratio was significantly higher in the high optPRS group compared to the low optPRS group ($p = 0.030$). In addition, p-tau181 levels were higher in the high optPRS group compared to low optPRS group ($p = 0.002$) (Figure 4E), consistent with the immunoblotting results. A correlation between the insoluble-to-soluble Aβ42 ratio and p-tau181 levels was also observed ($p = 0.040$), (Figure 4F). These results suggest that high PRS is associated with increased Aβ insolubility and tau phosphorylation.

4 | DISCUSSION

In this study, we modified the previously developed PRS[3] into optPRS, which demonstrated improved predictive performance for ADD and Aβ positivity. High optPRS was significantly associated with more rapid cognitive decline, especially in Aβ+ individuals. In addition, we confirmed that iPSC-derived cerebral organoids from patients with high optPRS was associated with increased Aβ insolubility and p-tau level compared to those from patients with low optPRS. Taken together, patients with AD and high optPRS, indicating genetic susceptibility to AD independent of *APOE*, exhibit a more rapid progression, and this phenomenon is replicated in individualized organoid models. Our findings reinforce the potential of the optPRS for clinical applications.

We successfully developed an optPRS by refining the SNP components and including Aβ biomarkers, creating a robust and accurate PRS model for ADD risk prediction, applicable to individuals of Korean ancestry. Previous PRS studies have focused predominantly on European populations with clinically diagnosed AD and often lacked

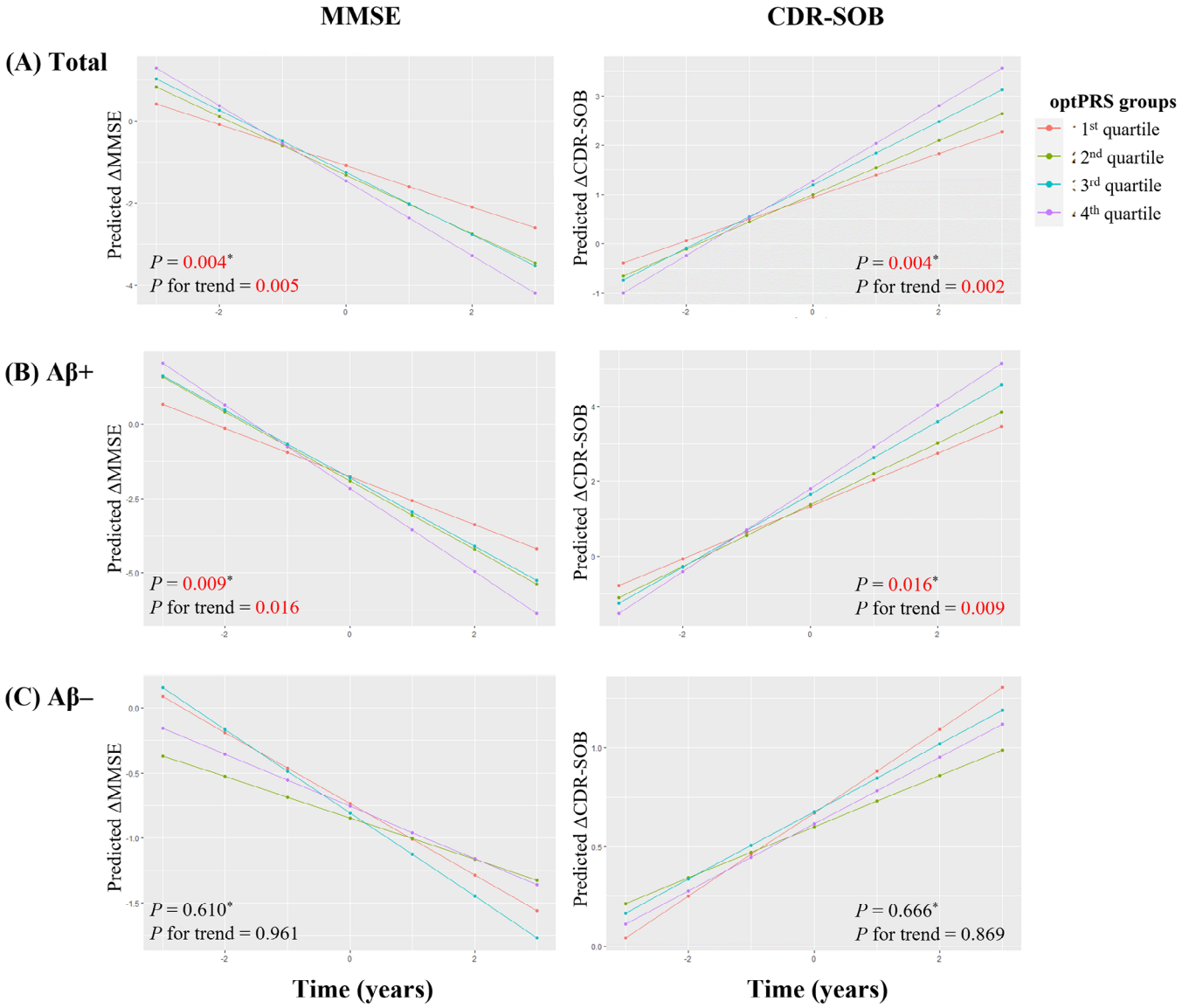


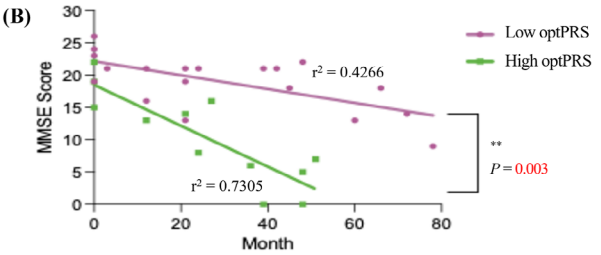
FIGURE 2 Effects of optPRS on cognitive trajectories. Participants with higher optPRS group showed more rapid cognitive decline and faster progression of disease severity, as measured by MMSE and CDR-SB, respectively. This association was more prominent in Aβ+ individuals. Lower K-MMSE scores indicate poorer cognitive function, whereas higher CDR-SB scores indicate worsening disease severity. *p*-values for first versus fourth quartile comparisons* and *p* for trend are shown in each panel. Aβ, amyloid beta; CDR-SB, Clinical Dementia Rating Sum of Boxes; CDR-SOB, Clinical Dementia Rating Sum of Boxes; K-MMSE, Korean Mini-Mental State Examination; MMSE, mini-mental state examination; optPRS, optimized polygenic risk score.

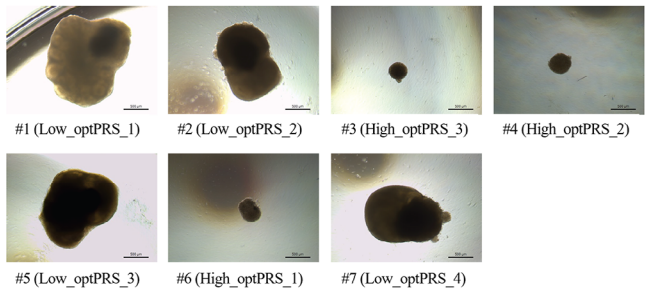
Aβ biomarkers (e.g., UK Biobank).[4] Although a French cohort study included Aβ data,[38] it was limited to CU individuals and validated within European-based initiatives, such as the Alzheimer's Disease Neuroimaging Initiative and the European Alzheimer's Disease Initiative studies. The optPRS demonstrated strong predictive performance in individuals with ADD and Aβ positivity, independent of the *APOE* genotype. By validating the optPRS in a Korean cohort and further demonstrating its association with ADD in Chinese participants from the UK Biobank, our study bridges the gap in the generalizability of our PRS models. However, further validation in other Asian groups is needed given the genetic diversity within East Asia. This emphasizes the importance of including diverse populations in AD genetic studies to reflect the complex genetic architecture of AD.

Furthermore, optPRS demonstrated its performance in predicting the prognosis of ADD, showing significant associations with cognitive trajectories as measured by K-MMSE and CDR-SB scores, particularly in Aβ+ participants. Although earlier studies primarily investigated the PRS in cross-sectional cohorts,[38,39] our study demonstrated a significant association between the PRS and cognitive decline in a longitudinal cohort, particularly in a Korean population. This highlights the broad applicability of PRS models that were originally constructed based on IGAP GWAS across diverse genetic backgrounds. A

(A)

optPRS group	ID	Sex	*APOE*	Onset Age	Aβ PET	optPRS (z-score)	Blinded number
Low optPRS (n = 4)	Low_optPRS_1	F	ε3/ε4	76	+	-0.00247 (-1.619)	#1
	Low_optPRS_2	F	ε3/ε4	55	+	0.00148 (-0.979)	#2
	Low_optPRS_3	F	ε3/ε4	58	+	-0.00474 (-1.985)	#5
	Low_optPRS_4	M	ε3/ε4	72	+	0.00420 (-0.539)	#7
High optPRS (n = 3)	High_optPRS_1	F	ε3/ε4	50	+	0.01479 (1.173)	#6
	High_optPRS_2	F	ε3/ε4	49	+	0.01815 (1.715)	#4
	High_optPRS_3	F	ε3/ε4	52	+	0.01454 (1.131)	#3





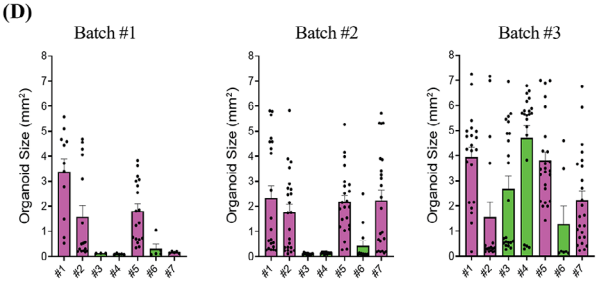


FIGURE 3 iPSC derivation and cerebral organoid generation from the low and high optPRS groups. (A) Demographic and clinical data of selected candidates for iPSC generation. (B) MMSE decline rates, showing more rapid cognitive decline in the high optPRS group compared to the low optPRS group ($p = 0.003$). (C) Representative images of cerebral organoids generated from low and high optPRS iPSC lines, derived from the second differentiation batch. (D) Cerebral organoid size distribution across three differentiation batches, with successful growth observed in all lines by the third batch except #6. iPSC, induced pluripotent stem cell; MMSE, Mini-Mental State Examination; optPRS, optimized polygenic risk score.

previous PRS model study focused exclusively on CU older adults and found that associations with cognitive decline were driven solely by the *APOE* genotype.[13] In contrast, our study included CU, aMCI, and ADD participants, and showed that the optPRS is associated with longitudinal cognitive decline regardless of *APOE* status, especially in Aβ+ individuals. Stratified analyses by cognitive status showed that in aMCI, higher optPRS was associated with faster progression of disease severity, suggesting stronger PRS effects at this stage. Our findings highlight the utility of optPRS in predicting cognitive decline over time and suggest that optPRS better reflects disease progression in the presence of Aβ pathology. These findings underscore the importance of stratifying patients by genetic risk and Aβ status for precise assessment of longitudinal cognitive trajectories in ADD.

Finally, we confirmed PRS-dependent increases in Aβ insolubility and tau hyperphosphorylation in an individualized cerebral organoid model. We generated iPSCs from the PBMCs of donors with high and low optPRS for AD and developed cerebral organoids. This approach is particularly useful for validating the utility of the optPRS, as it eliminates the influence of environmental factors and exhibits only the impact of genetic susceptibility. Although organoid models have been used extensively to investigate the role of *APOE* ε4 in AD,[18] the potential applications of PRSs in such models remain unexplored. Cerebral organoids generated from individuals with high optPRS exhibited a higher insoluble-to-soluble Aβ42 ratio and increased tau phosphorylation (p-tau217, p-tauS396, and p-tau181) compared to those from the low optPRS group. Although overall Aβ levels showed no significant differences, possibly because all participants were Aβ PET positive, Aβ42 in the high optPRS group was more concentrated, indicating enhanced aggregation and insolubility. Tau phosphorylation levels showed a significant correlation with the insoluble-to-soluble Aβ42 ratio, consistent with the hypothesis that Aβ aggregation accelerates tau pathology.[40] These results suggest that high optPRS levels contribute to disease-relevant biomarker expression in vitro. Furthermore, PBMC donors in the high optPRS group exhibited more severe cognitive decline than those in the low optPRS group, suggesting that PRS levels reflect disease aggressiveness. These data not only demonstrate the value of PRS-cerebral organoid models in elucidating the mechanisms driving AD pathology, but also highlight their potential to predict the onset and trajectory of AD symptoms. Moreover, cerebral organoid models stratified by PRS may serve as platforms for drug screening for novel disease-modifying therapies, supporting the development of personalized treatment strategies. With increasing advances in AD brain organoid technologies for precision medicine,[41–43] our findings—showing variation in AD-related pathology according to PRS—highlight their potential utility. These models may facilitate early identification of genetic risk individuals and enable evaluation of drug efficacy according to genetic risk profiles. Future studies should further characterize low and high optPRS organoids to identify effective treatments tailored to each subgroup.

Unexpectedly, we observed a line-specific defect in the formation of cerebral organoid from iPSCs in the high optPRS group. This phenomenon was consistent across the first two experimental batches despite the lack of significant differences in the morphology of all iPSCs lines. Notably, iPSC production and organoid development were conducted independently at separate institutions with blinded PRS information until all experiments were completed. Of interest, the defect in the high optPRS group lines was improved by the third batch,

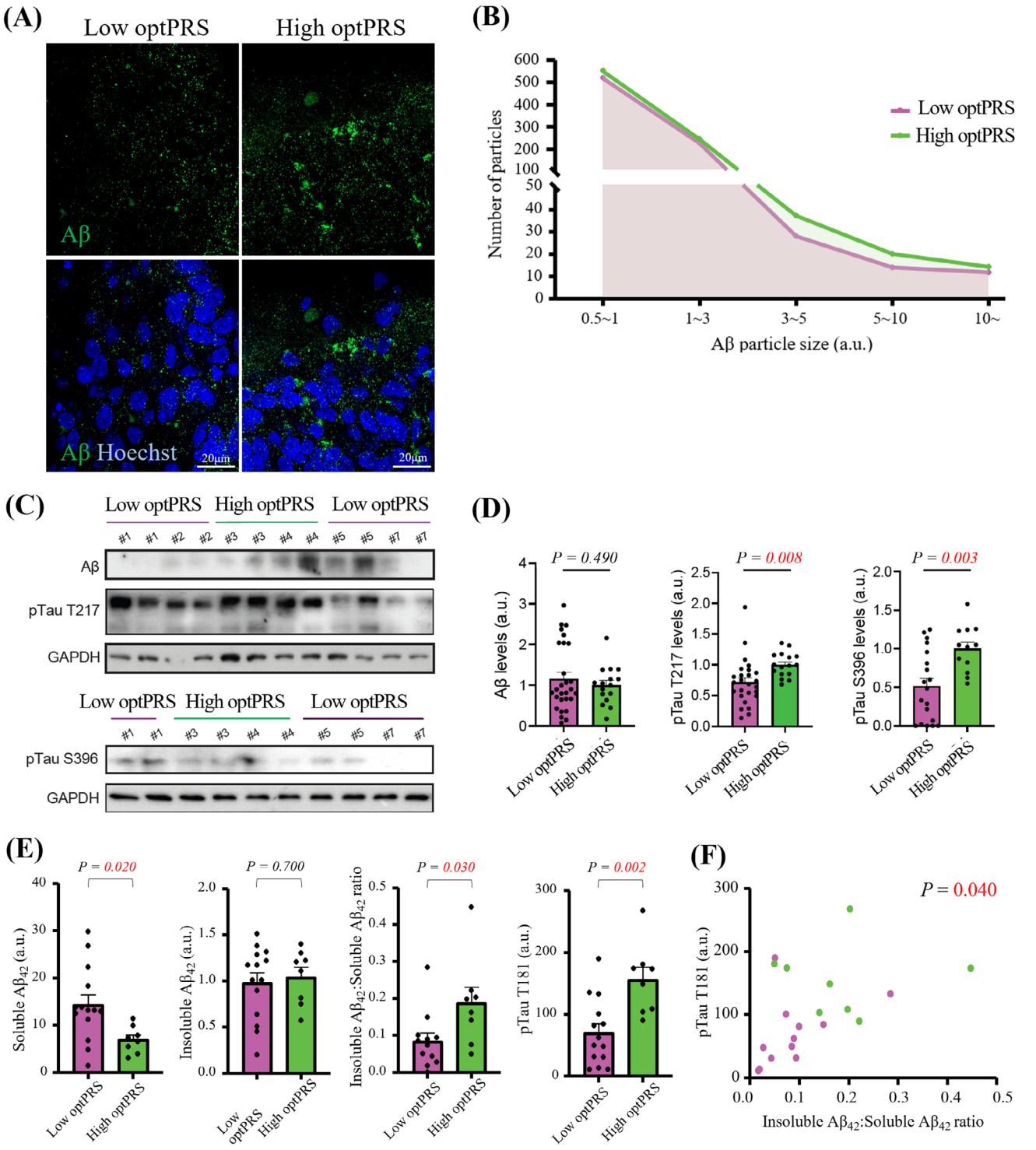


FIGURE 4 Analysis of AD-related pathological phenotypes, Aβ solubility, and tau phosphorylation in cerebral organoids derived from low and high optPRS groups. (A) Immunofluorescence images of Aβ aggregates (green) in cerebral organoids from low and high optPRS groups. Nuclei were counterstained with Hoechst (blue). Scale bar, 20 μm. (B) Distribution of Aβ particle sizes, showing larger particles in the high optPRS group. (C) Immunoblots of Aβ, p-tau217, and p-tauS396. (D) Quantification of blot signals revealed elevated p-tau217 and p-tauS396 levels in the high optPRS group compared to the low optPRS group. A total of 28 organoids from the low optPRS group and 16 organoids from the high optPRS group (4–8 organoids per individual) were analyzed. Group comparisons were made using unpaired *t*-tests. (E) ELISA results showing reduced soluble Aβ42, an increased insoluble-to-soluble Aβ42 ratio, and elevated p-tau181 levels in the high optPRS group. A total of 14 organoids from the low optPRS group and 8 organoids from the high optPRS group (2–4 organoids per individual) were analyzed. Group comparisons were made using unpaired *t*-tests. (F) Pearson's correlation analysis between the insoluble-to-soluble Aβ42 ratio and p-tau181 levels (purple dots, low optPRS; green dots, high optPRS). Aβ, amyloid beta; ELISA, enzyme-linked immunosorbent assay; optPRS, optimized polygenic risk score; p-tau, phosphorylated tau.

suggesting potential recovery through continuous cell transfer. This raises the possibility that cellular adaptation or conditioning over time may mitigate the initial defects in organoid formation. These early-stage formation defects in cerebral organoids from patients' PBMCs could serve as an indicator for predicting PRS and PRS-dependent pathological phenotypes.

This study has certain limitations. First, although we validated the association between optPRS and ADD using external data and its functional relevance using cerebral organoid models, we could not perform a trajectory analysis on Dataset 2 or 3 because of the lack of cognitive trajectory data. Future studies should focus on refining the PRS components and validating them across larger and more diverse populations to ensure generalizability. Second, the sample size for our cerebral organoid model was relatively small. In iPSC-derived brain organoid research, obtaining a sufficient number of independent donor samples is often challenging due to complexity of donor identification and iPSC generation. Although organoids within the same differentiation batch are considered technical replicates, they are frequently treated as independent experimental units in statistical analyses, as seen in previous studies.[44,45] In our high optPRS group, analyzable organoids were obtained exclusively from Batch 3, and thus our statistical analysis was performed using this single batch. Although this approach is consistent with prior studies operating under similar constraints, we acknowledge it as a limitation requiring cautious interpretation of our findings. Third, although our optPRS was constructed and optimized using European GWAS summary statistics, it is important to acknowledge the inherent limitations of applying PRS derived from European populations to non-European groups. Differences in linkage disequilibrium structure, allele frequencies, and population-specific genetic architecture can reduce the predictive accuracy and generalizability of PRS in East Asian populations. This limitation is widely recognized in the field and highlights the fundamental need to expand and strengthen GWAS and genetic research efforts in non-European populations, in order to improve risk prediction and ensure equitable advances in precision medicine across diverse groups.

In conclusion, we demonstrated the utility of optPRS as a valuable predictor of ADD and Aβ positivity, in addition to its significant associations with cognitive trajectory, particularly in Aβ+ individuals. Using iPSC-derived cerebral organoids, we confirmed that high PRS was associated with increased Aβ insolubility and tau hyperphosphorylation, highlighting the biological relevance of PRS in AD pathology. Our findings not only highlight the value of cerebral organoid models in elucidating the mechanisms driving AD pathology but also underscore their potential to predict AD progression and identify biomarkers for early disease detection. Integrating genetic risk assessments with cellular models is crucial for advancing personalized prediction of AD and for establishing platforms to screen effective, individualized therapeutic agents.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Any author disclosures are available in the Supporting Information.

CONSENT STATEMENT

All participants provided written informed consent at each center in South Korea, and the study was approved by the institutional review board of each center.

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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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