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Cerebrovascular disease in Alzheimer's disease: Brain structure as a critical mediator of cognitive decline

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ABSTRACT

Background: The co-occurrence of Alzheimer's disease and cerebrovascular disease is increasingly prevalent in aging populations, yet the mechanisms of their interaction remain incompletely understood. This study aims to investigate the associations between CVD and AD and their composite effects on cognitive function, identifying key mediating pathways in these relationships.

Methods: Participants underwent standardized clinical evaluations, detailed neuropsychological testing, and comprehensive neuropathological examinations. Structural equation modeling with multiple mediation analyses was employed to disentangle direct and indirect effects of vascular pathology on cognition and identify key mediating pathways. Relationships between specific cognitive domain assessments and whole brain and hippocampal volumes were analyzed, while interactions between traditional AD biomarkers (amyloid, tau) and vascular factors were examined.

Results: CVD substantially increased AD risk. Structural equation modeling revealed that vascular factors influence cognitive performance primarily through hippocampal atrophy, APOE genotype, and cerebral atrophy. Participants with concomitant AD +CVD pathology displayed a distinctive hybrid pattern of brain-cognition relationships, with stronger correlations between hippocampal atrophy and cognitive performance compared to pure AD or CVD cases. Pathway-specific analysis demonstrated that hippocampal atrophy served as the strongest mediator of vascular effects on cognition, followed by cerebral atrophy and APOE genotype.

Conclusion: Our findings demonstrate that cerebrovascular disease significantly increases the risk of Alzheimer's disease and substantially influences its clinical expression through multiple pathways, with structural brain changes serving as critical mediators of vascular effects on cognition. These results highlight the importance of addressing vascular health as an integral component of strategies to prevent and treat Alzheimer's disease and related cognitive disorders.

1. Introduction

Alzheimer's disease (AD) represents the most common cause of dementia worldwide, characterized by progressive cognitive decline and distinctive neuropathological features including Aβ plaques and neurofibrillary tangles [1]. Cerebrovascular disease (CVD), meanwhile, constitutes another major contributor to cognitive impairment in aging populations [2]. While traditionally viewed as distinct pathological entities, accumulating evidence suggests substantial overlap and potential interaction between AD and cerebrovascular pathologies [3], with population-based autopsy studies revealing that mixed pathologies are more common than pure presentations in elderly individuals with dementia [4].

The relationship between cerebrovascular factors and AD pathogenesis remains only partially understood [5], but recent studies have significantly advanced our knowledge of this complex interplay. Multiple pathways have been proposed through which vascular factors can influence neurodegeneration related to AD [6,7]. For instance, chronic hypoperfusion can lead to insufficient blood flow to critical brain regions, which can exacerbate neuronal damage and cognitive decline [8,9]. Additionally, blood-brain barrier dysfunction allows potentially harmful substances to enter the brain, triggering neuroinflammation, which is increasingly recognized as a key contributor to AD pathology [10]. Recent research has identified specific inflammatory markers, such as cytokines and chemokines, that relate closely to both cerebrovascular disease and neurodegenerative processes [11,12]. Furthermore, oxidative

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stress resulting from vascular injury has been implicated in accelerating amyloid-beta accumulation and tau phosphorylation, two hallmark features of AD [13,14].

Recent studies have shown that cerebrovascular pathology may lower the clinical threshold for AD symptoms, leading to earlier manifestation and greater cognitive impairment in individuals with concomitant vascular dysfunction [15]. For example, a 2022 study demonstrated that patients with both vascular lesions and AD pathology exhibited significantly worse cognitive outcomes compared to those with AD alone [16]. This increasing body of evidence underscores the critical importance of addressing cerebrovascular health in understanding, preventing, and treating Alzheimer's disease. By bridging the gap between cerebrovascular factors and AD, future interventions may enhance cognitive resilience and improve clinical outcomes for at-risk populations.

The potential mediating mechanisms linking cerebrovascular disease to cognitive outcomes in the context of AD remain poorly characterized. While traditional AD biomarkers including amyloid and tau pathologies represent well-established correlates of cognitive decline, the relative contributions of these markers versus structural brain changes in mediating vascular effects on cognition have not been comprehensively assessed [17]. Moreover, the potential synergistic interactions between vascular factors and white matter lesions—a common manifestation of small vessel cerebrovascular disease—warrant further investigation.

The National Alzheimer's Coordinating Center (NACC) database provides a unique opportunity to investigate these complex relationships through its comprehensive collection of standardized clinical, neuropsychological, and neuropathological data from Alzheimer's Disease Research Centers across the United States [16]. This resource enables robust analysis of multiple pathological features and their relationships to cognitive outcomes in well-characterized cohorts [18,19].

While the relationship between CVD and AD is increasingly recognized, significant research gaps remain. Existing studies have inadequately explored the complex interactions between vascular pathologies and neurodegeneration, often examining these factors in isolation. Our research addresses these limitations by employing advanced modeling techniques to comprehensively investigate the intricate mechanisms linking CVD and AD progression, providing novel insights into cognitive decline.

To this end, we aimed to determine the direct and indirect effects of cerebrovascular pathology on cognitive performance in AD, identifying key mediating pathways through structural equation modeling with multiple mediation analysis. Specifically, we examined whether vascular factors and white matter lesions impact cognitive outcomes through traditional AD pathological markers (amyloid and tau pathology), structural brain changes (hippocampal and cerebral atrophy, brain volume), or genetic factors (APOE genotype) [2,20]. By elucidating these mediating mechanisms, we sought to enhance understanding of the complex interplay between cerebrovascular and AD pathologies and potentially identify novel targets for therapeutic intervention aimed at preserving cognitive function in individuals with mixed pathologies.

2. Methods

2.1. Data source and participants

Data for this study were obtained from the NACC database, established in 1999 to facilitate collaborative research on AD and related disorders. The NACC database aggregates standardized clinical and neuropathological data collected by Alzheimer's Disease Research Centers (ADRCs) across the United States, funded by the National Institute on Aging (NIA). The database includes comprehensive information on participants' demographics, medical history, neurological examinations, neuropsychological test results, functional assessments, clinical diagnoses, APOE genotyping, neuroimaging findings, and neuropathological evaluations for those with available autopsy data.

For the current investigation, we included participants from the NACC database who had completed standardized clinical evaluations, cognitive assessments, and had available neuropathological data. All participants underwent comprehensive clinical assessments during life and subsequent neuropathological examinations at death. Only participants with complete data for cognitive measures, cerebrovascular pathology variables, and AD-related neuropathological markers were included in the analysis. For the etiologic diagnosis of cognitive disorders, Alzheimer's disease was identified using the code NACCALZD, where NACCALZD = 1 indicates the presence of Alzheimer's disease as the presumptive etiologic diagnosis of the cognitive disorder, while NACCALZD = 0 indicates its absence. Cerebrovascular disease was identified using the code CVD, where CVD = 1 indicates the presence of vascular brain injury (VBI) as an etiologic diagnosis, while CVD = 0 indicates no VBI as an etiologic diagnosis. The NACC database used in this study has received all necessary ethical approvals, and the research process strictly adheres to the principles of the Declaration of Helsinki and the guidelines of the ethics committees of all participating institutions. NACC ensures that informed consent was obtained from all participants or their legal representatives.

2.2. Inclusion and exclusion criteria

2.2.1. Inclusion criteria

1. Diagnosis Confirmation: Participants must be diagnosed with AD using the NACC code NACCALZD = 1
2. Clinical Assessment: Participants should have undergone comprehensive clinical evaluations, including cognitive and functional assessments, as well as neuropathological examinations at death.
3. Cerebrovascular Disease Assessment: Diagnosis of cerebrovascular disease must be confirmed with CVD = 1, indicating vascular brain injury.
4. Complete Data: Participants must have comprehensive data for all cognitive measures, cerebrovascular pathology variables, and AD-related neuropathological markers.

2.2.2. Exclusion criteria

1. Incomplete Data: Participants with missing or incomplete cognitive or neuropathological data will be excluded.
2. Non-completers: Individuals who did not finish required evaluations or assessments will be excluded.
3. Non-AD Diagnosis: Exclude participants diagnosed with other dementias or cognitive disorders not meeting AD or CVD criteria.
4. Lack of Autopsy: Participants must have neuropathological data from an autopsy; those without it will be excluded.

2.3. Cognitive assessment

Cognitive functioning was comprehensively evaluated using standardized neuropsychological assessments from the NACC Uniform Data Set. The Clinical Dementia Rating (CDR) scale, a semi-structured interview with both participants and informants, assessed impairment across six domains (memory, orientation, judgment/problem solving, community affairs, home/hobbies, and personal care), providing Global scores (0–3) and Sum of Boxes scores (0–18) to quantify dementia severity. Global cognitive status was measured using the Mini-Mental State Examination (MMSE, 0–30 points), assessing orientation, attention, calculation, recall, language, and visuospatial abilities, with lower scores indicating greater impairment. Language function was evaluated through the Boston Naming Test (confrontation naming of objects) and category fluency tasks (generating animal and vegetable names within one minute), which assess semantic knowledge, word retrieval, and cognitive processing speed. Memory capabilities were quantified via immediate and delayed recall tests, measuring both encoding and retrieval processes critical for episodic memory function. Attention and executive

functioning were assessed through Digit Span Forward (assessing attention span by repeating increasingly long number sequences), Digit Span Backward (evaluating working memory by repeating number sequences in reverse order), and Trail Making Test differential scores (TMT B-TMT A, isolating executive control by accounting for processing speed), providing a comprehensive profile of frontal-subcortical cognitive functions often affected in both AD and cerebrovascular disease.

2.4. Neuropathological assessment

Neuropathological evaluations were conducted by expert neuropathologists at NACC-affiliated centers following standardized protocols to ensure consistency across sites. Alzheimer's disease pathology was systematically quantified using Braak staging for neurofibrillary tangles (0=absent, I/II=transentorhinal, III/IV=limbic, V/VI=isocortical), reflecting the topographical progression of tau pathology from medial temporal structures to association cortices. Neuritic plaque burden was assessed using CREAD scores (0–3, reflecting none to frequent), providing a standardized measure of amyloid-associated neuritic degeneration. Thal phases (0–3) documented the anatomical progression of Aβ deposition from neocortex to brainstem structures. Cerebrovascular pathology evaluation included documentation of large vessel disease, small vessel disease, microinfarcts, and hemorrhages, with overall cerebrovascular disease categorized as present or absent based on established neuropathological criteria. White matter damage was specifically quantified through assessment of white matter rarefaction (classified as None, Mild, Moderate, or Severe), reflecting the extent of myelin loss and axonal damage associated with small vessel cerebrovascular disease. Brain structural integrity was assessed through whole brain weight measurements (in grams) and detailed regional atrophy evaluations of cerebral cortex, hippocampus, and specific lobar regions (frontal, temporal, parietal, occipital), each rated as None, Mild, Moderate, or Severe based on macroscopic examination. APOE genotyping was performed on DNA extracted from blood or brain tissue, with participants classified according to specific allele combinations ($\varepsilon2/\varepsilon2$, $\varepsilon2/\varepsilon3$, $\varepsilon2/\varepsilon4$, $\varepsilon3/\varepsilon3$, $\varepsilon3/\varepsilon4$, $\varepsilon4/\varepsilon4$) and carrier status, given the established role of the $\varepsilon4$ allele as a significant risk factor for both AD pathology and cerebrovascular disease.

2.5. Statistical analysis

Statistical analyses were performed to examine relationships between cerebrovascular pathology, AD pathological markers, and cognitive outcomes. Participants were initially categorized into four groups based on neuropathological findings: AD (N = 298), CVD (N = 17), AD+CVD (N = 81), and controls (N = 309). This classification was used for baseline characteristic comparisons and correlation analyses, with between-group differences evaluated using analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables. For risk factor assessment and mediation analyses, subjects were reclassified into two groups: AD group and non-AD group, allowing focused investigation of cerebrovascular disease as a potential risk factor for AD pathology.

Two primary cognitive outcomes were analyzed: MMSE as a measure of global cognitive function (with lower scores indicating greater impairment) and CDR Sum as an assessment of dementia severity (with higher scores indicating more severe impairment). Primary exposure variables included vascular factors (dichotomized as present or absent) and white matter lesions (rated as mild, moderate, or severe). An interaction term between vascular factors and white matter lesions was created to assess potential synergistic effects on cognitive outcomes and neuropathological markers.

We employed structural equation modeling (SEM) to conduct multiple mediation analyses examining seven potential mediating variables: tau pathology (Braak staging: 0 = none, 1 = stages I/II, 3 = stages III/IV, 5 = stages V/VI), amyloid pathology (CREAD score: 0–3), amyloid distribution (Thal phase: 0–3), brain volume (total cerebral volume), cerebral atrophy (mild/moderate/severe), hippocampal atrophy (mild/moderate/severe), and APOE genotype (coded as number of $\varepsilon4$ alleles: 0, 1, or 2). All analyses were adjusted for age and education level as established covariates influencing cognitive performance and disease risk.

For the mediation analysis, comprehensive models were constructed for each cognitive outcome that incorporated: exposure-mediator paths (a paths) representing effects of vascular factors, white matter lesions, and their interaction on each potential mediator; mediator-outcome paths (b paths) representing effects of each mediator on cognitive outcomes; and direct effect paths (c' paths) representing direct effects of exposures on outcomes independent of mediators. Specific indirect effects were computed as products of corresponding a and b coefficients, with total indirect effects calculated as sums of all specific indirect effects for each exposure. Total effects were determined by combining direct and total indirect effects. Full Information Maximum Likelihood estimation was employed to handle missing data, allowing inclusion of all available data points without listwise deletion. All statistical analyses were conducted using R (version 4.3.3) with specialized packages for structural equation modeling (lavaan), data manipulation (dplyr), visualization (ggplot2), and descriptive statistics (psych). Model fit was assessed using chi-square test and comparative fit indices, with significance levels set at $p < 0.05$ for all analyses.

3. Results

3.1. Participant demographics and group distribution

As shown in Table 1, the study included 705 participants: 298 (42.3 %) with AD, 17 (2.4 %) with CVD, 81 (11.5 %) with AD+CVD, and 309 (43.8 %) controls. Gender distribution differed significantly between groups (p = 8.60E-04, FDR = 1.70E-03), with more males in the AD group (54.7 %) than in controls (39.2 %). The mean age of all participants was 86.30 ± 7.86 years, with the AD +CVD group being oldest (88.23 ± 5.95 years). Educational attainment was similar across groups (overall mean: 15.80 ± 4.16 years). Cognitive status showed marked differences between groups (p = 1.70E-147, FDR = 2.10E-146), with most AD patients having dementia (70.8 %) or MCI (28.9 %), while all CVD and control participants had no cognitive impairment. In the concomitant group, 81.5 % had dementia and 18.5 % had MCI. APOE $\varepsilon4$ allele presence varied significantly (p = 1.20E-10, FDR = 5.90E-10), being more frequent in AD (48.7 %) and concomitant AD/CVD (38.3 %) groups compared to controls (22.0 %) and CVD patients (5.9 %). Clinical Dementia Rating scores also differed significantly (p = 2.20E-125, FDR = 2.40E-124), with most control (93.2 %) and CVD (94.1 %) participants scoring 0 (no dementia), while AD and concomitant groups showed predominantly higher scores indicating various dementia severity levels.

3.2. Cognitive assessment scores by group

Neuropsychological test performance varied markedly across diagnostic groups (Table 2). The AD group demonstrated the most impaired cognitive profile with the lowest MMSE scores (21.77 ± 5.85), compared to control (28.60 ± 1.43) and CVD (29.18 ± 0.95) groups, while the AD+CVD group showed similar impairment (22.53 ± 5.75). Memory function was severely affected in both AD and concomitant groups, with immediate recall scores of 6.63 ± 5.17 and 7.57 ± 5.23, and delayed recall scores of 4.94 ± 5.33 and 5.69 ± 5.10, respectively, substantially lower than CVD (immediate: 16.00 ± 3.61; delayed: 15.12 ± 3.87) and control groups (immediate: 14.92 ± 3.99; delayed: 13.89 ± 4.16). Working memory, as measured by digit span tests, showed similar patterns with AD and concomitant groups performing worse than CVD and

Table 1
Demographic and clinical characteristics of study participants.

Characteristics	AD (N = 298)	CVD (N = 17)	AD with CVD (N = 81)	Control (N = 309)	Total (N = 705)	P-value	FDR
Gender, N (%)						8.60E-04	1.70E-03
female	135 (19.15 %)	10 (1.42 %)	37 (5.25 %)	188 (26.67 %)	370 (52.48 %)		
male	163 (23.12 %)	7 (0.99 %)	44 (6.24 %)	121 (17.16 %)	335 (47.52 %)		
Age (years)	85.30 ± 8.77	87.82 ± 8.03	88.23 ± 5.95	86.67 ± 7.23	86.30 ± 7.86		
Years of education (years)	15.52 ± 2.78	16.18 ± 2.27	16.20 ± 2.72	15.94 ± 5.46	15.80 ± 4.16		
Cognitive Status, N (%)						1.70E-147	2.10E-146
Cognitive impairment (non-MCI)	1 (0.14 %)	0	0	0	1 (0.14 %)		
Dementia	211 (29.93 %)	0	66 (9.36 %)	0	277 (39.29 %)		
MCI	86 (12.20 %)	0	15 (2.13 %)	0	101 (14.33 %)		
NO cognition	0	17 (2.41 %)	0	309 (43.83 %)	326 (46.24 %)		
APOE ε4 allele, N (%)						1.20E-10	5.90E-10
0	153 (21.70 %)	16 (2.27 %)	50 (7.09 %)	241 (34.18 %)	460 (65.25 %)		
1	128 (18.16 %)	1 (0.14 %)	25 (3.55 %)	64 (9.08 %)	218 (30.92 %)		
2	17 (2.41 %)	0	6 (0.85 %)	4 (0.57 %)	27 (3.83 %)		
CDR Global, N (%)						2.20E-125	2.40E-124
0	1 (0.14 %)	16 (2.27 %)	2 (0.28 %)	288 (40.85 %)	307 (43.55 %)		
0.5	109 (15.46 %)	1 (0.14 %)	21 (2.98 %)	20 (2.84 %)	151 (21.42 %)		
1	117 (16.60 %)	0	36 (5.11 %)	1 (0.14 %)	154 (21.84 %)		
2	62 (8.79 %)	0	18 (2.55 %)	0	80 (11.35 %)		
3	9 (1.28 %)	0	4 (0.57 %)	0	13 (1.84 %)		
CDR Sum	6.06 ± 4.13	0.06 ± 0.17	6.77 ± 4.16	0.13 ± 0.53	3.40 ± 4.30		

Abbreviations: AD: Alzheimer's Disease, CVD: Cerebrovascular Disease, MCI: Mild Cognitive Impairment, APOE: Apolipoprotein E, CDR: Clinical Dementia Rating.

Table 2
Neuropsychological test performance across diagnostic groups.

Characteristics	AD (N = 298)	CVD (N = 17)	AD with CVD (N = 81)	Control (N = 309)	Total (N = 705)
MMSE	21.77 ± 5.85	29.18 ± 0.95	22.53 ± 5.75	28.60 ± 1.43	25.03 ± 5.51
Boston Naming	21.90 ± 7.03	27.18 ± 2.40	23.74 ± 5.21	27.52 ± 2.31	24.85 ± 5.68
Immediate recall	6.63 ± 5.17	16.00 ± 3.61	7.57 ± 5.23	14.92 ± 3.99	10.92 ± 6.16
Delayed recall	4.94 ± 5.33	15.12 ± 3.87	5.69 ± 5.10	13.89 ± 4.16	9.57 ± 6.49
Digit span forw. – trials	7.24 ± 2.09	8.94 ± 2.30	7.21 ± 1.96	8.11 ± 1.88	7.69 ± 2.04
Digit span forw. – length	6.09 ± 1.12	7.06 ± 1.03	6.00 ± 1.06	6.51 ± 1.08	6.30 ± 1.12
Digit span backw. – trials	4.81 ± 2.02	7.71 ± 2.23	5.00 ± 2.03	6.47 ± 1.87	5.68 ± 2.14
Digit span backw. – length	3.83 ± 1.25	5.24 ± 1.25	3.92 ± 1.16	4.78 ± 1.08	4.32 ± 1.25
Animals	11.13 ± 5.53	16.59 ± 5.65	12.70 ± 4.93	18.12 ± 4.89	14.69 ± 6.14
Vegetables	6.97 ± 3.94	10.53 ± 3.57	7.27 ± 3.57	12.51 ± 3.75	9.68 ± 4.66
TMT B-TMT A	61.99 ± 35.09	37.44 ± 7.20	58.42 ± 30.44	40.70 ± 16.55	50.53 ± 28.37

control groups in both forward and backward conditions. Semantic fluency was notably impaired in AD (animals: 11.13 ± 5.53; vegetables: 6.97 ± 3.94) and concomitant groups (animals: 12.70 ± 4.93; vegetables: 7.27 ± 3.57) compared to CVD (animals: 16.59 ± 5.65; vegetables: 10.53 ± 3.57) and control groups (animals: 18.12 ± 4.89; vegetables: 12.51 ± 3.75). Executive function, assessed by TMT B-TMT A, showed greater impairment in AD (61.99 ± 35.09) and concomitant (58.42 ± 30.44) groups compared to CVD (37.44 ± 7.20) and control groups (40.70 ± 16.55), indicating poorer cognitive flexibility and set-shifting abilities in patients with AD pathology.

3.3. Pathological findings across various assessment tools

Significant neuropathological differences were observed across diagnostic groups (Table 3). Braak staging revealed marked differences (p = 1.80E-22), with AD patients showing predominantly high-stage pathology (Braak V/VI: 52.3 % of AD cases) compared to controls, where most cases exhibited moderate pathology (Braak III/IV: 63.4 %). The CREAD neuritic plaque assessment similarly demonstrated significant differences (p = 1.80E-19), with AD patients showing higher scores (CREAD 2–3: 59.1 %) while controls predominantly had minimal plaque pathology (CREAD 0: 51.5 %). Thal amyloid phase distribution also varied significantly (p = 3.50E-17), with 67.8 % of AD cases showing advanced phase 3 amyloid deposition compared to only 31.7 % of controls.

While vascular pathology was nearly universal across all groups (99.43 % overall), white matter rarefaction severity differed significantly (p = 2.00E-04), with AD +CVD showing the highest proportion of severe rarefaction (19.8 %). Mean brain weight was lowest in the CVD group (1134.76 ± 139.33 g) and highest in controls (1202.00 ± 134.35 g). Cerebral cortical atrophy patterns varied significantly (p = 1.10E-20), with moderate-to-severe atrophy observed in 50.0 % of AD cases and 61.7 % of concomitant cases, compared to only 20.4 % of controls. Hippocampal atrophy showed the most significant group differences (p = 1.40E-24), with severe atrophy in 19.5 % of AD cases and 22.2 % of concomitant cases, but only 1.9 % of controls. Lobar atrophy was significantly more common (p = 1.20E-04) in AD (15.4 %) and concomitant groups (14.8 %) compared to controls (5.2 %), illustrating the extensive structural brain changes associated with Alzheimer's disease pathology.

3.4. Association between cerebrovascular pathology and Alzheimer's risk

CVD was significantly associated with increased risk of AD across all models (Supplementary materials: Table S1). In the unadjusted analysis (Model 1), CVD was associated with nearly 5-fold higher risk of AD (HR = 4.94, 95 % CI: 2.93-8.80, p = 1.01E-08). After adjustment for demographic factors and APOE genotype (Model 2), the association strengthened (HR = 5.71, 95 % CI: 3.31–10.39, p = 1.94E-09), with male gender (HR = 1.99, p = 8.99E-05) and APOE ε4 allele presence (one allele: HR = 3.20, p = 4.67E-10; two alleles: HR = 6.93, p = 6.80E-04) emerging as significant risk factors, while education showed a modest protective effect (HR = 0.93, p = 3.17E-02).

In the fully adjusted model (Model 3), which accounted for all demographic, genetic, and neuropathological variables, the association be-

Table 3
Neuropathological findings across diagnostic groups.

Characteristics	AD (N = 298)	CVD (N = 17)	AD with CVD (N = 81)	Control (N = 309)	Total (N = 705)	p-value	FDR
Braak, N (%)						1.80E-22	1.60E-21
0	6(0.85 %)	2(0.28 %)	0	2(0.28 %)	10(1.42 %)		
Braak I/ II	35(4.96 %)	2(0.28 %)	12(1.70 %)	67(9.50 %)	116(16.45 %)		
Braak III/IV	101(14.33 %)	12(1.70 %)	34(4.82 %)	196(27.80 %)	343(48.65 %)		
Braak V/VI	156(22.13 %)	1(0.14 %)	35(4.96 %)	42(5.96 %)	234(33.19 %)		
CREAD, N (%)						1.80E-19	1.30E-18
0	52(7.38 %)	12(1.70 %)	28(3.97 %)	159(22.55 %)	251(35.60 %)		
1	70(9.93 %)	0	17(2.41 %)	67(9.50 %)	154(21.84 %)		
2	87(12.34 %)	2(0.28 %)	22(3.12 %)	23(3.26 %)	134(19.01 %)		
3	89(12.62 %)	3(0.43 %)	14(1.99 %)	60(8.51 %)	166(23.55 %)		
Thal, N (%)						3.50E-17	2.10E-16
0	23(3.26 %)	6(0.85 %)	13(1.84 %)	87(12.34 %)	129(18.30 %)		
1	37(5.25 %)	4(0.57 %)	18(2.55 %)	62(8.79 %)	121(17.16 %)		
2	36(5.11 %)	5(0.71 %)	13(1.84 %)	62(8.79 %)	116(16.45 %)		
3	202(28.65 %)	2(0.28 %)	37(5.25 %)	98(13.90 %)	339(48.09 %)		
vascular, N (%)						0.63	0.63
NO	1(0.14 %)	0	0	3(0.43 %)	4(0.57 %)		
YES	297(42.13 %)	17(2.41 %)	81(11.49 %)	306(43.40 %)	701(99.43 %)		
White matter rarefaction, N (%)						2.00E-04	5.90E-04
Mild	149(21.13 %)	10(1.42 %)	30(4.26 %)	124(17.59 %)	313(44.40 %)		
Moderate	48(6.81 %)	1(0.14 %)	17(2.41 %)	51(7.23 %)	117(16.60 %)		
None	89(12.62 %)	3(0.43 %)	18(2.55 %)	104(14.75 %)	214(30.35 %)		
Severe	12(1.70 %)	3(0.43 %)	16(2.27 %)	30(4.26 %)	61(8.65 %)		
Whole brain weight, N (%)	1176.74 ± 137.14	1134.76 ± 139.33	1181.82 ± 152.93	1202.00 ± 134.35	1187.33 ± 138.33		
cerebral cortex atrophy, N (%)						1.10E-20	8.50E-20
Mild	141(20.00 %)	15(2.13 %)	23(3.26 %)	197(27.94 %)	376(53.33 %)		
Moderate	118(16.74 %)	1(0.14 %)	41(5.82 %)	63(8.94 %)	223(31.63 %)		
None	8(1.13 %)	1(0.14 %)	8(1.13 %)	49(6.95 %)	66(9.36 %)		
Severe	31(4.40 %)	0	9(1.28 %)	0	40(5.67 %)		
hippocampus atrophy, N (%)						1.40E-24	1.40E-23
Mild	105(14.89 %)	7(0.99 %)	29(4.11 %)	144(20.43 %)	285(40.43 %)		
Moderate	105(14.89 %)	6(0.85 %)	27(3.83 %)	48(6.81 %)	186(26.38 %)		
None	30(4.26 %)	4(0.57 %)	7(0.99 %)	111(15.74 %)	152(21.56 %)		
Severe	58(8.23 %)	0	18(2.55 %)	6(0.85 %)	82(11.63 %)		
lobar atrophy, N (%)						1.20E-04	5.00E-04
NO	252(35.74 %)	17(2.41 %)	69(9.79 %)	293(41.56 %)	631(89.50 %)		
YES	46(6.52 %)	0	12(1.70 %)	16(2.27 %)	74(10.50 %)		

tween CVD and AD risk further increased (HR = 7.72, 95 % CI: 3.88–16.16, p = 1.77E-08). This model revealed that beyond CVD, significant independent predictors of AD included age (HR = 1.03, p = 4.86E-02), male gender (HR=2.44, p = 5.54E-04), APOE ε4 carrier status (one allele: HR = 2.25, p = 9.27E-04), neuritic plaque burden (CREAD C1: HR = 2.76, p = 6.04E-03; CREAD C2: HR=4.37, p = 1.11E-03), moderate cerebral cortex atrophy (HR = 3.16, p = 2.04E-04), and severe hippocampal atrophy (HR = 8.91, p = 2.10E-05). Notably, the effect of APOE ε4 homozygosity was attenuated and no longer significant in the fully adjusted model, suggesting its effects may be mediated through the included neuropathological variables. These findings demonstrate that CVD remains a robust and significant risk factor for AD even after comprehensive adjustment for established demographic, genetic, and neuropathological factors, with the association strengthening rather than weakening with more extensive adjustment.

3.5. Correlation analysis of pathological markers and cognitive test performance

This comprehensive correlation analysis reveals distinct patterns of association between neuropathological markers and cognitive performance across diagnostic groups (Fig. 1). In the AD group, APOE ε4 allele showed the strongest correlations with cognitive measures (Eta = 0.937 for Boston Naming, p < 0.001), followed by significant associations between Braak staging and global cognitive status (CDR Global: Eta = 0.021, p < 0.001; CDR Sum: Eta = 0.026, p < 0.000). Amyloid pathology markers (CREAD, Thal) demonstrated modest but significant correlations with multiple cognitive domains. Structural measures including cerebral cortical atrophy (CDR Sum: Eta = 0.021, p < 0.001) and hippocampal atrophy (MMSE: Eta = 0.021, p < 0.001) were significantly associated with cognitive performance. Notably, whole brain weight correlated significantly with all cognitive measures in the AD group.

In the CVD group, the pattern of associations differed substantially, with whole brain weight emerging as the strongest correlate of cognitive performance (Eta values 0.214–0.446, all p < 0.001). White matter rarefaction uniquely showed significant correlations with global cognitive measures (CDR Global: Eta = 0.070, p < 0.001; CDR Sum: Eta = 0.079, p < 0.001) and attention measures (digit span forward trials: Eta = 0.041, p = 0.001). Traditional AD markers showed minimal associations with cognition in the CVD group, except for CREAD with global measures (CDR Global: Eta = 0.032, p = 0.00392).

The concomitant AD +CVD group displayed a hybrid pattern with remarkably strong correlations between hippocampal atrophy and cognitive performance (CDR Sum: Eta = 0.173, p < 0.001; MMSE: Eta = 0.115, p < 0.001), cerebral cortical atrophy and global cognition (CDR Sum: Eta = 0.165, p < 0.001), and extraordinarily strong correlations between whole brain weight and all cognitive measures (Eta values 0.232–0.528, all p < 0.001). Both AD-specific pathology markers (Braak, CREAD) and vascular pathology measures (white matter rarefaction) showed significant correlations with cognition in this group.

3.6. Mediation analysis of cerebrovascular factors on cognitive performance in AD pathology

Vascular factors demonstrated substantial indirect effects on cognitive performance, with a negative impact on MMSE (−1.865) and positive effect on CDR Sum (1.502), indicating that cerebrovascular pathology primarily influences cognition through mediating mechanisms rather than direct pathways. White matter lesions showed parallel

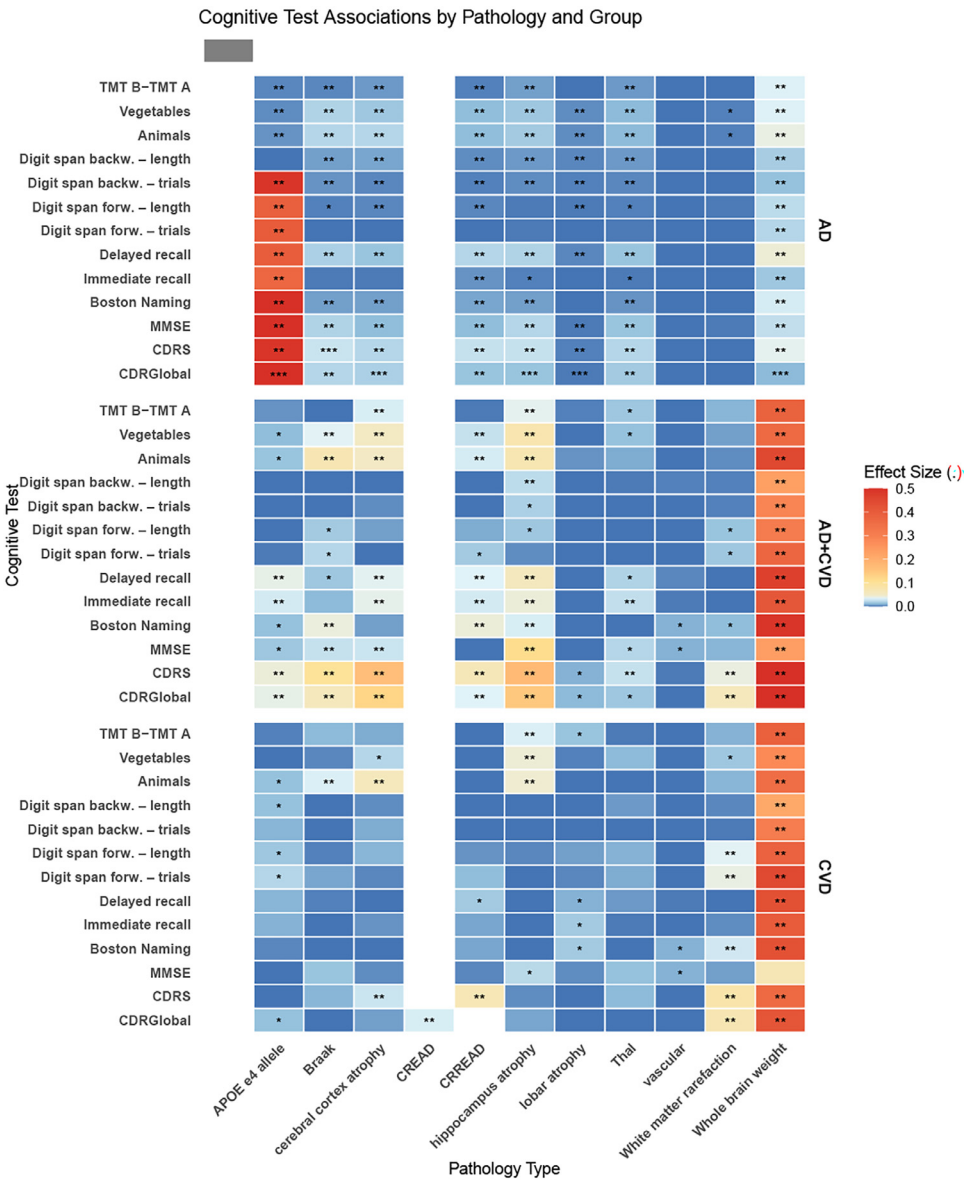

Fig. 1. Relationship between cognitive test scores and neuropathological features in Alzheimer's disease and cerebrovascular disease.

but weaker effects (MMSE: −0.298; CDR Sum: 0.223), with interaction effects mirroring white matter lesion patterns exactly, suggesting overlapping pathophysiological processes or synergistic mechanisms.

The analysis of exposure-mediator relationships (Supplementary materials: Table S2) revealed that vascular factors most strongly associated with amyloid pathology (CREAD: 1.378), followed by APOE genotype (0.565), hippocampal atrophy (0.482), and Thal amyloid plaques (0.456). This pattern supports significant cerebrovascular contributions to multiple AD pathological features. White matter lesions primarily impacted brain volume (−11.171), with considerably weaker associations with amyloid (CREAD: 0.230) and tau pathology (Braak: 0.165), indicating differential mechanisms between vascular factors and white matter pathology.

Examination of mediator-outcome relationships (Supplementary materials: Table S3) identified hippocampal atrophy as the strongest determinant of cognitive performance (MMSE: −1.333; CDR Sum: 1.083), followed by cerebral atrophy (MMSE: −0.821; CDR Sum: 1.108) and APOE genotype (MMSE: −0.950; CDR Sum: 0.692). Traditional AD biomarkers showed moderate (Braak, Thal) to minimal (CREAD) cognitive effects, suggesting structural brain changes may more directly influence cognitive outcomes than molecular pathology markers.

Pathway-specific analysis (Table 4) demonstrated that vascular factors impacted cognition predominantly through hippocampal atrophy (MMSE: −0.656; CDR Sum: 0.522), APOE genotype (MMSE: −0.536; CDR Sum: 0.391), and cerebral atrophy (MMSE: −0.294; CDR Sum: 0.397). White matter lesions operated through similar pathways but with substantially weaker effects. Notably, structural brain changes served as stronger mediators than traditional AD pathological markers, particularly for white matter lesions, highlighting the critical role of neuroanatomical integrity in the cerebrovascular-cognitive relationship.

Our mediation analysis revealed complex relationships between vascular factors and cognitive outcomes (Supplementary materials: Table S4). For MMSE scores, vascular factors showed complete mediation (100.20 %) primarily through hippocampal atrophy (35.2 %), APOE genotype (28.8 %), and brain atrophy (15.8 %), while white matter lesions exhibited negative mediation via hippocampal and brain atrophy. Regarding CDR Sum outcomes, vascular factors' effects were substantially mediated (96.60 %) through hippocampal atrophy (34.7 %), brain atrophy (26.4 %), and APOE (26.0 %), whereas white matter lesions and their interaction with vascular factors displayed pronounced mediation effects (518.60 %), mainly through brain atrophy (188.4 %) and hippocampal atrophy (111.6 %). These findings highlight that vas-

Table 4
Specific indirect effects of cerebrovascular pathology on cognitive outcomes through multiple mediating pathways.

Mediating pathway	MMSE vascular indirect effect	MMSE white matter indirect effect	MMSE interaction indirect effect	CDR sum vascular indirect effect	CDR sum white matter indirect effect	CDR sum interaction indirect effect
Through Braak Score	−0.097	−0.091	−0.091	0.031	0.029	0.029
Through CREAD Score	−0.113	−0.019	−0.019	−0.041	−0.007	−0.007
Through Thal Score	−0.17	−0.042	−0.042	0.202	0.05	0.05
Through Brain Volume	0	−0.049	−0.049	0	0.041	0.041
Through Brain Atrophy	−0.294	−0.061	−0.061	0.397	0.081	0.081
Through Hippocampal Atrophy	−0.656	−0.063	−0.063	0.522	0.048	0.048
Through APOE	−0.536	0.027	0.027	0.391	−0.02	−0.02
Total Indirect Effect	−1.865	−0.298	−0.298	1.502	0.223	0.223

cular pathology influences cognitive function predominantly by inducing structural brain changes and interacting with genetic factors, with the substantial mediation percentages for CDR Sum outcomes emphasizing the crucial role of brain structural alterations in translating vascular pathology to clinical dementia severity.

4. Discussion

Our study demonstrates significant interactions between CVD and AD, with CVD substantially increasing AD risk. Structural equation modeling revealed that vascular factors influence cognitive performance primarily through hippocampal atrophy, APOE genotype, and cerebral atrophy. Participants with concomitant AD +CVD pathology displayed a distinctive hybrid pattern of brain-cognition relationships, with stronger correlations between hippocampal atrophy and cognitive performance compared to pure AD or CVD cases.

Recent clinical research has increasingly recognized the significance of mixed cerebrovascular and AD pathologies in aging populations [21,22]. Some study demonstrated that cerebrovascular pathology co-occurs with primary AD pathology in most cases of late-onset dementia, with neuroimaging studies showing that cerebrovascular lesions directly impact disease progression and cognitive expression [23]. This phenomenon may explain the variance in cognitive symptoms among individuals with similar amyloid and tau burdens [24,25]. A recent study further reinforced this relationship, showing that vascular burden interacts with Aβ accumulation to accelerate cognitive decline, particularly in individuals in early disease stages [26]. Their longitudinal analysis revealed that those with both vascular pathology and amyloid positivity showed faster progression to dementia than those with either pathology alone [27].

A study analyzed data from the National Alzheimer's Coordinating Center to examine associations between cerebrovascular disease and AD pathology with cognitive decline. They found that white matter hyperintensities, a common marker of small vessel cerebrovascular disease, independently predicted cognitive trajectory even after controlling for AD biomarkers [28]. Similarly, Morales et al. (2024) demonstrated that small vessel cerebrovascular disease was significantly associated with cognitive impairment in prospective Alzheimer's clinical trial participants [17], further supporting our findings that vascular pathology represents an important and potentially modifiable risk factor for AD-related cognitive decline.

The mechanistic relationships between CVD and AD pathologies appear to involve complex interactions between vascular factors, genetic susceptibility, and traditional AD biomarkers [29,30]. Our study found that the APOE ε4 allele is significantly more prevalent in both AD and concomitant AD +CVD groups compared to controls and pure CVD patients, suggesting shared genetic vulnerability. Recent evidence indicates that APOE plays a crucial role in both disorders through multiple mechanisms [31]. APOE ε4 leads to blood-brain barrier dysfunction preceding cognitive decline, establishing a potential vascular pathway through which this genetic variant increases AD risk [32,33]. Tau and apolipoprotein E modulate cerebrovascular tight junction integrity independent of cerebral amyloid angiopathy, suggesting that these proteins affect vascular function through multiple pathways [34,35].

The structural integrity of the hippocampus is critical for cognitive function, and its atrophy is considered a central feature of cognitive decline in AD and related disorders [36,37]. Existing studies have indicated that hippocampal atrophy is not only associated with the worsening of AD pathologies but is also closely related to cerebrovascular health [38,39]. Research shows that chronic ischemia and insufficient cerebral blood flow may lead to neuronal damage in the hippocampal region, thereby accelerating cognitive decline [40,41]. Moreover, cerebrovascular damage can promote neuroinflammation and oxidative stress, leading to neurodegeneration in the hippocampus [42,43].

As evidenced in this study, AD patients with cerebrovascular pathology often experience more significant hippocampal atrophy and its negative impact on cognitive performance. Hippocampal atrophy predicts declines in cognitive ability and suggests that hippocampal atrophy may be a primary mediating mechanism for the indirect effects of cerebrovascular pathology on cognition [44]. Our analyses further support this notion, indicating that hippocampal atrophy plays a particularly significant role in the relationship between cerebrovascular factors and cognitive decline. Changes in the structure of the hippocampus could serve as a pivotal target for future therapeutic interventions.

Individuals carrying the APOE ε4 allele may experience blood-brain barrier dysfunction, leading to increased risks of neuroinflammation and neuronal damage [45,46]. This phenomenon may cause these individuals to exhibit more pronounced symptoms in the early stages of cognitive decline [47]. Epidemiological studies have shown that APOE ε4 is associated with a more rapid rate of cognitive decline, and individuals with one or two APOE ε4 alleles typically demonstrate more significant cognitive deterioration in clinical presentations compared to those with other genotypes [48,49].

Additionally, research has found that the presence of APOE ε4 may affect the interactions with other pathological markers in the brain, such as beta-amyloid and tau proteins [50,51]. Specifically, APOE ε4 carriers may be more susceptible to structural brain damage related to vascular injury and Alzheimer's disease (e.g., hippocampal atrophy), which further affects their cognitive performance [52,53]. Therefore, when analyzing the relationship between small vessel disease and cognitive function, it is essential to consider the genotype of APOE ε4. This genotype is not only a hereditary risk factor for Alzheimer's disease but may also modulate the effects of other pathological markers on cognitive abilities by influencing brain structure and function.

The interaction between Aβ and cerebrovascular function represents another critical mechanism [54]. Aβ directly contributes to neurovascular dysfunction by impairing blood vessel reactivity, promoting inflammation, and accelerating vascular degeneration [55]. Aβ oligomers induce cerebrovascular dysfunction through pericyte-mediated endothelial damage, establishing a direct mechanistic link between this hallmark AD protein and vascular pathology [56]. Notably, this relationship appears bidirectional, as studies of cerebrovascular phenotypes in mouse

models of AD reveal vascular alterations that not only precede but potentially accelerate both amyloid and tau deposition [57].

Tau pathology, while traditionally examined primarily within the context of AD, demonstrates significant and meaningful interactions with vascular factors. Research has identified distinct patterns of Aβ, tau, and APOE accumulation when comparing AD-tau with other tauopathies, with cerebrovascular factors actively modulating these complex relationships [58–60]. Our mediation analyses strongly support these observations, demonstrating that vascular factors correlate robustly with both tau (Braak staging) and amyloid (CREAD, Thal) pathologies. These findings collectively suggest that cerebrovascular disease may serve as a critical mediator of both core pathological processes underlying Alzheimer's disease progression [61].

Our findings highlight the critical role of structural brain changes, particularly hippocampal atrophy and generalized cerebral atrophy, in mediating the effects of vascular pathology on cognitive outcomes [62]. Specifically, our pathway-specific analysis demonstrated that hippocampal atrophy served as the strongest mediator of vascular effects on cognition, followed by cerebral atrophy and APOE genotype. These findings align with recent research demonstrating that blood-brain barrier dysfunction in AD leads to increased neuroinflammation, accelerated neurodegeneration, and consequent brain atrophy [63,64].

The preferential involvement of the hippocampus in these pathological processes explains the prominent memory deficits observed in our concomitant AD +CVD group. Hippocampal integrity serves as a critical mediator between various pathological processes and cognitive function, with both AD and cerebrovascular pathologies converging on this vulnerable structure [62,65]. The strong correlation between whole brain weight and all cognitive measures in our concomitant AD +CVD group further underscores the importance of preserving overall brain structural integrity in the face of mixed pathologies.

Neuroimaging studies have offered insights into these relationships. Multiple neuroimaging techniques in AD research and highlighted that structural changes detectable through MRI often precede clinical symptoms by several years [66,67], with mixed vascular and AD pathologies showing distinctive patterns of regional atrophy and white matter damage [68]. These structural changes represent the result of multiple upstream pathological processes, including amyloid deposition, tau aggregation, vascular damage, and neuroinflammation, making them powerful integrative biomarkers of disease progression and cognitive outcomes [69–71].

Our study has notable strengths, including a comprehensive assessment of participants through standardized clinical evaluations, neuropsychological testing, and neuropathological examinations, which provided valuable insights into the links between vascular factors and AD. We employed advanced statistical methods, such as structural equation modeling, to clarify the effects of vascular pathology on cognition, and we focused on specific cognitive domains to better understand these impacts. Additionally, the inclusion of traditional AD biomarkers and structural brain integrity measures allowed for a thorough evaluation of relevant pathways.

However, our research has limitations, such as a cross-sectional design that restricts causal inferences and temporal relationships, necessitating longitudinal studies. The small sample size for pure CVD cases (n = 17) relative to the AD (n = 298) and control (n = 309) groups may have limited statistical power. Moreover, our reliance on categorical assessments rather than continuous measures may have reduced sensitivity to detect subtle differences. Also, we did not assess relevant factors like inflammation and specific vascular biomarkers. Lastly, findings from a clinical cohort may not fully generalize to the broader aging population with mixed cerebrovascular and AD pathologies.

Our findings highlight a significant link between CVD and AD, emphasizing the need for an integrated clinical approach. Vascular factors can worsen cognitive decline, particularly through hippocampal atrophy. Clinicians should integrate cardiovascular assessments in cognitive evaluations and personalize treatment plans based on factors like APOE genotype. Lifestyle changes—such as better diet, physical activity, and smoking cessation—along with vascular-targeting medications, are crucial for neuroprotection. Ongoing neuropsychological assessments for at-risk patients will allow timely treatment adjustments. Understanding the interplay between CVD and AD enables healthcare providers to implement proactive strategies to prevent cognitive decline and improve the quality of life for aging individuals.

Future research should prioritize longitudinal designs to capture the dynamic relationships among vascular function, AD biomarkers, and cognitive performance over time. By conducting repeated assessments, researchers can elucidate the temporal sequence of events and their interactions within the context of aging. Incorporating additional biomarkers that reflect inflammation, oxidative stress, and blood-brain barrier integrity is crucial, as these factors may significantly influence the pathophysiology of AD and its association with vascular health. Understanding how these biological processes interconnect can provide deeper insights into potential interventions. Furthermore, implementing therapeutic studies focused on vascular health is essential to determine whether improving vascular function can alter the trajectory of AD progression. Such studies should evaluate the effects of lifestyle modifications, pharmacologic treatments, and other interventions on cognitive outcomes and AD biomarkers. Ultimately, this multifaceted approach will enhance our understanding of the mechanisms linking vascular health and neurodegeneration, paving the way for more effective strategies in preventing and managing AD.

5. Conclusion

Our findings demonstrate that cerebrovascular disease significantly increases the risk of Alzheimer's disease and substantially influences its clinical expression through multiple pathways, with structural brain changes serving as critical mediators of vascular effects on cognition. These results highlight the importance of addressing vascular health as an integral component of strategies to prevent and treat Alzheimer's disease and related cognitive disorders.

Abbreviation List

AD	Alzheimer's Disease
CVD	Cerebrovascular Disease
MCI	Mild Cognitive Impairment
APOE	Apolipoprotein E
CDR	Clinical Dementia Rating
CDR Global	Clinical Dementia Rating Global Score
CDR Sum	Clinical Dementia Rating Sum Score
MMSE	Mini-Mental State Examination
NACC	National Alzheimer's Coordinating Center
CREAD	Neuritic Plaque Assessment Score
Thal	Amyloid Deposition Staging
Aβ	Amyloid Beta
SEM	Structural Equation Modeling
TMT	Trail Making Test
HR	Hazard Ratio
FDR	False Discovery Rate
CI	Confidence Interval

Declarations

Ethics approval and consent to participate

Not applicable. All data were downloaded from the internet.

Human ethics and consent to participate declarations

Not applicable.

Participate declaration

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The data used in the present study are all publicly available at https://naccdata.org/requesting-data/nacc-data.

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Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

CRediT authorship contribution statement

Chao Tang: Data curation, Conceptualization. **Yaqi Ding:** Formal analysis, Data curation. **Jiaxin Yang:** Conceptualization. **Dian He:** Writing – review & editing, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100209.

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