Association Between White Matter Hyperintensity Severity and Cognitive Impairment According to the Presence of the Apolipoprotein E (*APOE*) ε4 Allele in the Elderly: Retrospective Analysis of Data From the CREDOS Study

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ABSTRACT

Objective: To investigate the effect of white matter hyperintensity (WMH) severity on cognitive function according to presence of the apolipoprotein E (*APOE*) ε4 allele.

Method: From participants in a nationwide, multicenter, hospital-based cohort study of dementia by the Clinical Research Center for Dementia of South Korea (November 2005 to December 2011), data for 5,077 elderly subjects (mean [SD] age = 71.37 [8.40] years) who had available data for *APOE* genotype and WMH severity were studied retrospectively. We used the diagnostic criteria for mild cognitive impairment proposed by Petersen et al; the diagnostic criteria for vascular dementia included in *DSM-IV*; and, for probable Alzheimer's disease, the criteria issued by the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association. WMH severity was evaluated using modified criteria of Fazekas et al and Scheltens et al using T2 axial or fluid-attenuated inversion recovery magnetic resonance images, yielding 3 groups for WMH severity level. *APOE* genotype was determined by analysis of venous blood, and all participants were classified into 2 groups depending on presence or absence of the *APOE* ε4 allele. The Seoul Neuropsychological Screening Battery-Dementia Version was used for all subjects. Cognitive impairment, classified by 6 cognitive test scores, was the primary outcome measure. Using multiple logistic regression, we investigated which cognitive domains were associated with WMH severity and the *APOE* ε4 allele, and, using analysis of covariance, we examined the interaction effects of these 2 factors on cognitive test scores.

Results: After multivariable adjustments, logistic regression analyses showed that WMH severity was associated with higher odds of cognitive impairment on frontal/executive function tests in both *APOE* ε4 carriers (odds ratio [OR] = 2.49; 95% CI, 1.65–3.76) and noncarriers (OR = 2.36; 95% CI, 1.83–3.03). WMH severity was not significantly associated with memory function in *APOE* ε4 carriers: for verbal memory, ε4 noncarriers had an OR of 1.44 (95% CI, 1.13–1.84), and ε4 carriers had an OR of 1.36 (95% CI, 0.87–2.04); for visuospatial memory, ε4 noncarriers had an OR of 1.86 (95% CI, 1.45–2.37), and ε4 carriers had an OR of 1.35 (95% CI, 0.89–2.04). Moreover, a significant interaction effect between *APOE* ε4 and WMH severity was confirmed on memory tests by analysis of covariance (verbal memory: $F = 3.40$, $P = .033$; visuospatial memory: $F = 8.49$, $P < .001$).

Conclusions: Severe WMHs appear to be predominantly associated with frontal/executive dysfunction, irrespective of *APOE* ε4 allele presence. WMH severity and *APOE* ε4 had an interactive effect on memory function, with WMH severity affecting memory impairment only in *APOE* ε4 noncarriers.

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The volume of white matter hyperintensities (WMHs) in brain magnetic resonance imaging has been reported to be a predictor of cognitive decline among the elderly in several prospective studies.[1,2] White matter changes related to cognitive impairment seem to result from chronic microvascular disease and hypoperfusion[3]; however, not every person with vascular risk factors has WMH lesions. This fact suggests that WMH burden might be related to the interaction between vascular risk factors and other factors, such as genetic variation.[4–6]

A possible candidate for such a genetic factor is the apolipoprotein E (*APOE*) ε4 allele. The mechanism by which the presence of the *APOE* ε4 allele exerts its effect on cognitive impairment remains yet unclear; such means might be related to its effect on amyloid-β deposition[7,8] along with an increased vulnerability to chronic hypoperfusion of the white matter.[9,10] Thus, some studies have found an association between *APOE* ε4 and ischemic cerebrovascular disease[11] as well as Alzheimer's disease.[12]

However, despite various studies, the association between the *APOE* ε4 allele and WMHs remains controversial.[5,13,14] The different patterns of cognitive impairment associated with *APOE* ε4 and WMH severity were also reported in separate studies.[15,16] Moreover, relatively little is known about WMH severity–related cognitive phenotypes between the elderly who carry the *APOE* ε4 allele versus those who do not. If the *APOE* genotype interacts with severity of WMHs, then it is possible that *APOE* ε4 carriers will show dissociated patterns of neuropsychological presentation compared to noncarriers. In the present study, we investigated the effect of WMH severity on cognitive phenotype according to the presence of *APOE* ε4 allele.

METHOD

Subjects

This study, which began in November 2005, was part of an ongoing, nationwide multicenter study of dementia by the Clinical Research Center for Dementia of South Korea (CREDOS), designed

to assess the occurrence and risk factors of cognitive disorders. The CREDOS study, registered on ClinicalTrials.gov (identifier: NCT01198093), recruited patients from university-affiliated hospitals who were diagnosed with normal cognition, subjective memory impairment, mild cognitive impairment, vascular cognitive impairment, Alzheimer's disease, or subcortical ischemic vascular dementia. In the CREDOS study, we used the diagnostic criteria for vascular dementia included in the Fourth Edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*),[17] the diagnostic criteria for probable Alzheimer's disease issued by the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA),[18] and the diagnostic criteria for mild cognitive impairment proposed by Petersen et al.[19] A more detailed description of CREDOS is available elsewhere.[20] Of CREDOS participants from November 2005 to December 2011, we retrospectively analyzed the data for 5,077 patients who had available data for *APOE* genotype and WMH severity. None of the subjects presented any of the following exclusion criteria: (1) history of significant hearing or visual impairment rendering participation in the interview difficult; (2) neurologic disorders (eg, territorial infarction, intracranial hemorrhage, brain tumor, and hydrocephalus); (3) psychiatric disorders (eg, schizophrenia, mental retardation, severe depression, or mania); (4) history of use of psychotropic medications or psychoactive substances other than alcohol; (5) physical illnesses or disorders that could interfere with the clinical study, such as cardiac diseases, respiratory illnesses, uncontrolled diabetes, uncontrolled hypertension, malignancy, hepatic diseases, and renal diseases; or (6) white matter changes other than ischemia, or other clinical causes of dementia except Alzheimer's disease or subcortical ischemic vascular dementia. This study was approved by the institutional review boards of the participating centers, and informed consent was obtained from all subjects.

Clinical Evaluations

The clinical evaluation form was filled out by informants after they received appropriate instructions. The clinical evaluation form included questionnaires related to (1) basic demographic characteristics; (2) history of cognitive decline according to the caregiver; (3) the Korean version of the Mini-Mental State Examination[21]; (4) the Clinical Dementia Rating[22]; (5) the 15-item Geriatric Depression Scale[23]; and (6) past medical history, including cerebrovascular risk factors, such as hypertension, diabetes mellitus, hyperlipidemia, and cardiac diseases (coronary heart disease, arrhythmia, heart failure, and valvular heart disease). Cerebrovascular risk factors were rated positive if the patient had been previously diagnosed with an associated disease or if the patient was currently under medical treatment for the disease. A standardized neuropsychological battery, the Seoul Neuropsychological Screening Battery-Dementia Version (SNSB-D)[24] was used to assess all participants. The SNSB-D includes tests of language, verbal/nonverbal memory, attention, and frontal/executive function domains. These domains were assessed using the following tests[24]: the Korean short version of the Boston Naming Test (K-BNT) for language, the Digit Span Test-backward for attention function, the Rey Complex Figure Test-delayed recall (RCFT-delayed recall) for visuospatial memory, the Seoul Verbal Learning Test-delayed recall (SVLT-delayed recall) for verbal memory, and the Stroop Test-color reading and Controlled Oral Word Association Test (COWAT) for frontal/executive function. We used age-specific, gender-specific, and education-specific norms for each test based on SNSB-D reference standards. Cognitive test scores below the 16th percentile of the norm were classified as *cognitive impairment*.[24]

Clinical Points

- Clinicians should consider the volume of white matter hyperintensities (WMHs), which seem to be predominantly associated with frontal/executive dysfunction irrespective of the presence of the apolipoprotein E (*APOE*) ε4 allele, in the elderly.
- On the other hand, *APOE* ε4 carriers perform worse on memory tests, and it is only *APOE* ε4 noncarriers that show some relationship between WMH severity and memory performance among the elderly.
- Current evidence supports the disassociation of *APOE* and WMHs relative to cognitive performance, a finding that may be helpful for clinicians in predicting the characteristics of cognitive impairment as affected by the *APOE* ε4 allele or WMHs.

Visual Rating of White Matter Hyperintensities

Magnetic resonance imaging was conducted in accordance with the protocol for magnetic resonance imaging acquisition developed for the CREDOS study. Magnetic resonance imaging scans included transaxial T2-weighted, T1-weighted, gradient-echo, fluid-attenuated inversion recovery, and coronal T1-weighted images. The severity of WMHs was evaluated according to the modified criteria of Fazekas et al[25] and Scheltens et al[26] using the T2 axial or fluid-attenuated inversion recovery images. White matter hyperintensities were separately examined in periventricular white matter and deep white matter. Additionally, periventricular white matter and deep white matter ratings were combined to provide a final measurement of the severity of ischemia. Deep white matter lesions were divided into D1 (deep white matter < 10 mm), D2 (deep white matter from 10 mm to < 25 mm), and D3 (deep white matter ≥ 25 mm) groups on the basis of the greatest diameter of the lesions. Periventricular white matter lesions were divided into P1 (cap and band < 5 mm), P2 (cap and band from 5 mm to < 10 mm), and P3 (cap and band ≥ 10 mm) groups on the basis of the size of the cap and band, which were perpendicular

Table 1. Characteristics of Subjects Grouped According to White Matter Hyperintensity Severity (N = 5,077)

Variable	White Matter Hyperintensity Severity			χ^2 or F^a	*P*
	Mild (n = 3,194)	Moderate (n = 1,263)	Severe (n = 620)		
Age, mean ± SD, y	69.33 ± 8.65	74.69 ± 6.77	75.06 ± 8.40	280.27	< .001
Gender, female, n (%)	2,232 (69.9)	858 (67.9)	428 (69.0)	1.64	.441
Education, mean ± SD, y	8.31 ± 5.39	6.98 ± 5.35	6.98 ± 5.41	36.34	< .001
Illness duration, mean ± SD, mo	34.48 ± 31.68	34.20 ± 32.08	40.43 ± 34.94	9.11	< .001
Physical illness, n (%)					
Hypertension	1,314 (41.1)	714 (56.5)	425 (68.5)	201.65	< .001
Diabetes	536 (16.8)	260 (20.6)	113 (18.2)	8.96	.011
Hyperlipidemia	416 (13.0)	153 (12.1)	80 (12.9)	0.68	.711
Cardiac disease	270 (8.5)	143 (11.3)	55 (8.9)	9.00	.011
CDR score, n (%)				225.48	< .001
0	155 (4.9)	25 (2.0)	11 (1.8)		
0.5	2,319 (72.6)	813 (64.4)	317 (51.1)		
1	556 (17.4)	328 (26.0)	192 (31.0)		
2	146 (4.6)	81 (6.4)	79 (12.7)		
3	18 (0.6)	16 (1.3)	21 (3.4)		
APOE allele type, n (%)				42.89	< .001
ε2/ε2	11 (0.3)	5 (0.4)	1 (0.2)		
ε2/ε3	231 (7.2)	136 (10.8)	62 (10.0)		
ε3/ε3	1,782 (55.8)	699 (55.3)	384 (61.9)		
ε2/ε4	42 (1.3)	20 (1.6)	11 (1.8)		
ε3/ε4	938 (29.4)	337 (26.7)	150 (24.2)		
ε4/ε4	190 (5.9)	66 (5.2)	12 (1.9)		
K-MMSE score, mean ± SD	23.01 ± 5.54	21.33 ± 5.74	20.35 ± 6.17	79.71	< .001
GDS-15 score, mean ± SD	5.86 ± 4.25	6.42 ± 4.48	6.54 ± 4.61	11.40	< .001

[a] χ^2 for categorical variables; *F* for continuous variables.
Abbreviations: *APOE* = apolipoprotein E, CDR = Clinical Dementia Rating, GDS-15 = 15-item Geriatric Depression Scale, K-MMSE = Korean Mini-Mental State Examination.

to and horizontal to the ventricle, respectively. These results were combined to provide a total measurement of mild (D1P1, D1P2), moderate (neither mild nor severe; D1P3, D2P1, D2P2, D2P3, D3P1, D3P2), or severe (D3P3), yielding 3 groups for WMH severity level. The interrater reliability for the periventricular white matter and deep white matter hyperintensities was good (intraclass correlation coefficient of 0.73–0.91).

APOE Genotyping

Genomic DNA was extracted from venous blood. Blood samples from each individual were collected in EDTA tubes, and the *APOE* genotype was determined using the polymerase chain reaction.[27] All participants were classified into 2 groups, depending on the presence or absence of the *APOE* ε4 allele.

Statistical Analysis

The general characteristics of the participants were examined on the basis of WMH severity and presence of *APOE* ε4 allele using χ^2 tests, Mantel-Haenszel χ^2 test, independent *t* test, and analysis of variance as appropriate. To identify which cognitive domains were specifically associated with WMH severity and *APOE* ε4, we conducted multivariate logistic regression analyses with adjustment for various potential confounders. Then, an analysis of covariance was conducted to confirm the interaction effects of the presence of the *APOE* ε4 allele and WMH severity on cognitive test scores. Following the analysis of covariance, we performed a post hoc test to compare the differences in cognitive test scores between *APOE* ε4 carriers and noncarriers for each level of WMH severity. To minimize the potential confounding effects, the following covariates were entered into the adjusted model, consistent with previous literature[11,28,29]: age, gender, education, illness duration, cerebrovascular risk factors (hypertension, diabetes, hyperlipidemia, cardiac disease), and depression score. A *P* value of < .05 was considered statistically significant. In post hoc tests, type I error was adjusted using the Bonferroni method (.05/3 = .0167). We used SPSS software, version 18.0 (SPSS Inc, Chicago, Illinois), for all analyses.

RESULTS

Characteristics

Of the 5,077 subjects, 1,559 were men (30.7%) and 3,518 were women (69.3%). The subjects' mean (SD) age was 71.37 (8.40) years. Mean (SD) educational level was 7.82 (5.42) years. Subjects were classified by WMH severity level as mild (n = 3,194; 62.9%), moderate (n = 1,263; 24.9%), or severe (n = 620; 12.2%). Table 1 lists the characteristics of the participants in each WMH severity group. The *APOE* ε4 carriers numbered 1,766 (ε4/ε4 allele pair = 268 [15.2%]; ε3/ε4 = 1,425 [80.7%]; ε2/ε4 = 73 [4.1%]), and noncarriers totaled 3,311 (ε3/ε3 = 2,865 [86.5%]; ε2/ε3 = 429 [13.0%]; ε2/ε2 = 17 [0.5%]). The general characteristics of the subjects are described in Table 2 according to the presence of the *APOE* ε4 allele. In the group with severe WMHs, a greater number of *APOE* ε4 noncarriers were observed (Mantel-Haenszel test: $\chi^2 = 18.67$, $P < .001$).

Table 2. Characteristics of Subjects Grouped According to Presence of the *APOE* ε4 Allele (N = 5,077)

Variable	*APOE* ε4 Noncarriers (n = 3,311)	*APOE* ε4 Carriers (n = 1,766)	χ^2 or t[a]	*P*
Age, mean ± SD, y	71.44 ± 8.62	71.23 ± 7.97	0.85	.397
Gender, female, n (%)	2,322 (70.1)	1,196 (67.7)	3.13	.079
Education, mean ± SD, y	7.66 ± 5.42	8.12 ± 5.40	−2.88	.004
Illness duration, mean ± SD, mo	34.60 ± 33.54	36.10 ± 29.73	−1.55	.120
Physical illness, n (%)				
Hypertension	1,647 (49.7)	806 (45.6)	7.77	.008
Diabetes	632 (19.1)	277 (15.7)	9.07	.003
Hyperlipidemia	409 (12.4)	240 (13.6)	1.58	.217
Cardiac disease	334 (10.1)	134 (7.6)	8.60	.003
CDR score, n (%)			33.79	< .001
0	147 (4.4)	44 (2.5)		
0.5	2,301 (69.5)	1,148 (65.0)		
1	644 (19.5)	432 (24.5)		
2	190 (5.7)	116 (6.6)		
3	29 (0.9)	26 (1.5)		
APOE allele type, n (%)			NA	NA
ε2/ε2	17 (0.5)	0		
ε2/ε3	429 (13.0)	0		
ε3/ε3	2,865 (86.5)	0		
ε2/ε4	0	73 (4.1)		
ε3/ε4	0	1,425 (80.7)		
ε4/ε4	0	268 (15.2)		
White matter hyperintensity severity, n (%)			18.67	< .001
Mild	2,024 (61.1)	1,170 (66.3)		
Moderate	840 (25.4)	423 (24.0)		
Severe	447 (13.5)	173 (9.8)		
K-MMSE score, mean ± SD	22.76 ± 5.68	21.34 ± 5.79	8.44	< .001
GDS-15 score, mean ± SD	6.18 ± 4.34	5.89 ± 4.39	2.27	.023

[a] χ^2 for categorical variables; *t* for continuous variables.
Abbreviations: *APOE* = apolipoprotein E, CDR = Clinical Dementia Rating, GDS-15 = 15-item Geriatric Depression Scale, K-MMSE = Korean Mini-Mental State Examination, NA = not applicable.

Identification of Cognitive Domains Associated With White Matter Hyperintensity Severity and the *APOE* ε4 Allele

We examined the association between WMH severity and cognitive impairment according to the presence of the *APOE* ε4 allele by multiple logistic regression analyses. Analysis showed that patients with severe WMHs performed significantly worse than those with mild WMHs in language, attention, and, particularly, frontal/executive functions, as measured by the K-BNT, the Digit Span Test-backward, the Stroop Test, and the COWAT, respectively, regardless of *APOE* ε4 allele presence (Table 3). We found that, after adjusting for various potential confounders, only *APOE* ε4 noncarriers showed a significant association between WMH severity and memory impairment, as measured by the SVLT-delayed recall and RCFT-delayed recall tests (see Table 3).

We also conducted multiple logistic regression analyses to evaluate the association between *APOE* ε4 and cognitive impairment. After adjustment for age, gender, education, illness duration, cerebrovascular risk factors (hypertension, diabetes, hyperlipidemia, and cardiac disease), and depression score, the *APOE* ε4 allele was found to be more associated with both verbal and visuospatial memory impairment compared to other cognitive domains (SVLT-delayed recall: odds ratio [OR] = 2.47 [95% CI, 2.15–2.83]; RCFT-delayed recall: OR = 2.30 [95% CI, 2.01–2.63]; K-BNT: OR = 1.29 [95% CI, 1.14–1.46]; Digit Span Test-backward: OR = 1.17 [95% CI, 1.03–1.33]; Stroop Test: OR = 1.30 [95% CI, 1.15–1.47]; COWAT: OR = 1.42 [95% CI, 1.25–1.61]). The results were also confirmed in the fully adjusted model including WMH severity (SVLT-delayed recall: OR = 2.50 [95% CI, 2.18–2.88]; RCFT-delayed recall: OR = 2.35 [95% CI, 2.06–2.69]; K-BNT: OR = 1.31 [95% CI, 1.15–1.49]; Digit Span Test-backward: OR = 1.20 [95% CI, 1.06–1.36]; Stroop Test: OR = 1.35 [95% CI, 1.19–1.53]; COWAT: OR = 1.48 [95% CI, 1.30–1.68]) (see Supplementary eTable 1, available at PSYCHIATRIST.COM). The overall results were unchanged even before and after accounting for the confounding effects of hypertension in these analyses.

Interactive Effects of *APOE* ε4 and White Matter Hyperintensity Severity on Cognitive Function

Using the analysis of covariance, we tested the interaction effects of *APOE* ε4 and WMH severity on cognitive test scores after adjusting for confounding variables. As shown in Table 4, interactive effects were observed on the SVLT-delayed recall and RCFT-delayed recall tests (SVLT-delayed recall: $F = 3.40$, $P = .033$, $R^2 = 0.23$; RCFT-delayed recall: $F = 8.49$, $P < .001$, $R^2 = 0.25$). In post hoc tests, *APOE* ε4 carrier and noncarrier groups showed a significant difference in estimated least-squares means for SVLT-delayed recall and RCFT-delayed recall test scores for the severe WMH level compared to the mild WMH level (SVLT-delayed recall: mild [$t = 13.0$, $P < .001$], moderate [$t = 7.5$, $P < .001$], severe [$t = 2.5$,

Table 3. Effect of White Matter Hyperintensity (WMH) Severity on Cognitive Impairment According to Presence of the *APOE* ε4 Allele (N = 5,077)[a]

Function	Test	WMH Severity	*APOE* ε4 Noncarriers (n = 3,311) OR (95% CI)	*P*	*APOE* ε4 Carriers (n = 1,766) OR (95% CI)	*P*
Language	K-BNT	Mild	Reference		Reference	
		Moderate	1.27 (1.06–1.52)	.011	0.97 (0.76–1.25)	.840
		Severe	1.66 (1.31–2.10)	< .001	1.24 (0.86–1.80)	.251
Verbal memory	SVLT-delayed recall	Mild	Reference		Reference	
		Moderate	1.13 (0.94–1.36)	.193	1.15 (0.86–1.55)	.350
		Severe	1.44 (1.13–1.84)	.003	1.36 (0.87–2.04)	.183
Visuospatial memory	RCFT-delayed recall	Mild	Reference		Reference	
		Moderate	1.15 (0.96–1.37)	.141	1.16 (0.88–1.53)	.301
		Severe	1.86 (1.45–2.37)	< .001	1.35 (0.89–2.04)	.163
Attention	Digit Span Test-backward	Mild	Reference		Reference	
		Moderate	1.22 (1.01–1.46)	.040	1.25 (0.97–1.60)	.085
		Severe	1.92 (1.52–2.42)	< .001	2.04 (1.43–2.90)	< .001
Frontal/executive function	Stroop Test-color reading	Mild	Reference		Reference	
		Moderate	1.54 (1.28–1.85)	< .001	1.82 (1.40–2.37)	< .001
		Severe	2.36 (1.83–3.03)	< .001	2.49 (1.65–3.76)	< .001
	COWAT	Mild	Reference		Reference	
		Moderate	1.44 (1.20–1.72)	< .001	1.24 (0.96–1.60)	.107
		Severe	2.65 (2.06–3.41)	< .001	2.46 (1.60–3.78)	< .001

[a]Adjusted by age, gender, education, illness duration, cerebrovascular risk factors (hypertension, diabetes, hyperlipidemia, cardiac disease), and depression score.
Abbreviations: *APOE* = apolipoprotein E, COWAT = Controlled Oral Word Association Test, K-BNT = Korean Boston Naming Test, RCFT = Rey Complex Figure Test, SVLT = Seoul Verbal Learning Test.

Table 4. Cognitive Test Scores According to *APOE* ε4 Allele Presence and White Matter Hyperintensity Severity (N = 5,077)

Variable	Mild (n = 3,194), Mean ± SD (n[a])	Moderate (n = 1,263), Mean ± SD (n[a])	Severe (n = 620), Mean ± SD (n[a])
K-BNT score			
APOE ε4 noncarrier	38.02 ± 12.33 (861)	33.06 ± 11.79 (457)	31.66 ± 12.22 (271)
APOE ε4 carrier	36.56 ± 11.83 (584)	31.68 ± 11.66 (240)	30.55 ± 12.24 (103)
SVLT-delayed recall score[b]			
APOE ε4 noncarrier	3.54 ± 3.16 (1,000)	2.55 ± 2.75 (493)	2.18 ± 2.61 (279)
APOE ε4 carrier	2.26 ± 2.99 (812)	1.34 ± 2.08 (315)	1.43 ± 2.24 (130)
RCFT-delayed recall score[b]			
APOE ε4 noncarrier	8.94 ± 7.45 (958)	6.47 ± 6.38 (467)	5.16 ± 5.69 (292)
APOE ε4 carrier	5.75 ± 6.67 (806)	3.86 ± 5.12 (301)	3.88 ± 4.63 (124)
Digit Span Test-backward score			
APOE ε4 noncarrier	3.13 ± 1.40 (589)	2.80 ± 1.31 (309)	2.49 ± 1.27 (200)
APOE ε4 carrier	3.06 ± 1.24 (384)	2.64 ± 1.27 (162)	2.28 ± 1.31 (85)
Stroop Test-color reading score			
APOE ε4 noncarrier	64.46 ± 30.47 (965)	51.84 ± 28.00 (515)	42.80 ± 27.74 (311)
APOE ε4 carrier	59.43 ± 30.89 (630)	46.34 ± 29.00 (287)	39.47 ± 27.47 (124)
COWAT score			
APOE ε4 noncarrier	11.97 ± 4.94 (949)	10.08 ± 4.48 (494)	8.58 ± 4.16 (317)
APOE ε4 carrier	11.16 ± 4.74 (663)	9.51 ± 4.48 (270)	7.80 ± 3.71 (129)

[a]Number of subjects with an abnormal cognitive test.
[b]$P < .05$; analysis of covariance showing interactive effects of the *APOE* ε4 allele and white matter hyperintensity severity on cognitive function, after adjusting for age, gender, education, illness duration, cerebrovascular risk factors (hypertension, diabetes, hyperlipidemia, cardiac disease), and depression score.
Abbreviations: *APOE* = apolipoprotein E, COWAT = Controlled Oral Word Association Test, K-BNT = Korean Boston Naming Test, RCFT = Rey Complex Figure Test, SVLT = Seoul Verbal Learning Test.

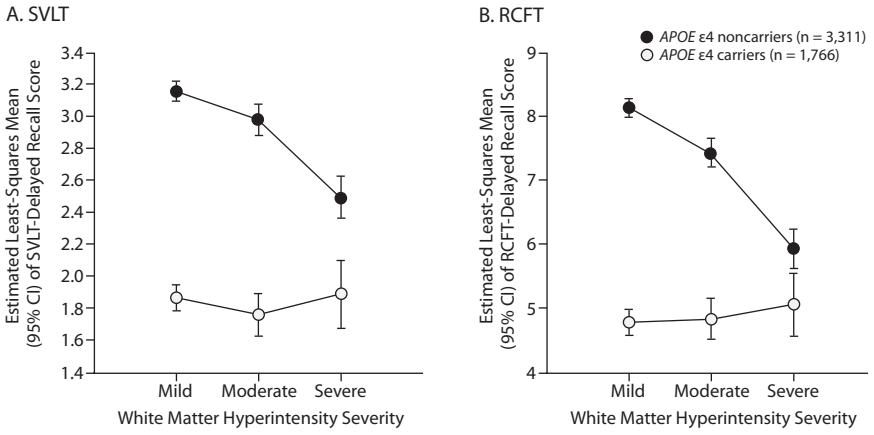
$P = .042$]; RCFT-delayed recall: mild [$t = 14.5$, $P < .001$], moderate [$t = 6.9$, $P < .001$], severe [$t = 1.5$, $P = .397$]) (Figure 1).

DISCUSSION

The purpose of this study was to investigate the effect of WMH severity on cognitive function according to *APOE* genotype. In this hospital-based population with cognitive impairment, patients with large WMH volume performed significantly worse in cognitive domains generally associated with frontal lobe systems regardless of *APOE* ε4 allele presence. White matter hyperintensity severity was associated with naming and memory functions only in *APOE* ε4 noncarriers, but to a lesser extent in comparison to general frontal lobe function.

Consistent with previous studies,[16,30] our results showed a strong relationship between high-level WMH volume and poorer frontal/executive functions, which might result

Figure 1. Estimated Least-Squares Means of the (A) SVLT-Delayed Recall Test and (B) RCFT-Delayed Recall Test for Each Level of White Matter Hyperintensity Severity According to Presence of the *APOE* ε4 Allele



Abbreviations: *APOE* = apolipoprotein E, RCFT = Rey Complex Figure Test, SVLT = Seoul Verbal Learning Test.

from significantly reduced frontal lobe metabolism, synaptic dysfunction, altered sensory information process, and neurotransmitter depletion, as suggested by previous associations with executive function.[31–33] Our results also revealed that the effects of increased WMH volumes on poorer executive performance were robust in both *APOE* ε4 carriers and noncarriers. For memory and naming functions, WMH severity was found to be associated with these functions only in *APOE* ε4 noncarriers. Even when the suppressor effects of cerebrovascular risk factors such as hypertension, well-correlated with WMHs,[5] were considered together, the overall results were unaffected. On the other hand, even after we adjusted the analysis for various confounding variables, including WMH severity level, the *APOE* ε4 carriers in this study were impaired to a greater extent than noncarriers on delayed recall measures, a finding usually considered to be dependent on the medial temporal lobe memory system. Several studies have reported that *APOE* ε4 carriers display poorer memory function,[34–37] as well as smaller hippocampal or other medial temporal lobe volumes,[38–42] than noncarriers. In agreement with previous studies,[14,15,20] our results additionally found that the effects of *APOE* ε4 allele presence on memory function might be independent of WMH burden.

These results might suggest the possibility of distinct processes between the predominant effect of WMHs on frontal/executive function and the predominant effect of the *APOE* ε4 allele on memory function. Despite various studies,[5,13,14] the association between the *APOE* ε4 allele and WMHs remains controversial. Some prospective population-based studies[5,6] reported that patients with *APOE* ε4 and concomitant vascular diseases had more severe WMHs and atrophy. It could be hypothesized that the *APOE* ε4 allele promoted vascular deposition of the amyloid-β peptide,[43,44] and cerebral amyloid angiopathy related to cerebral blood flow reduction might result in elevated WMH burden.[10,45–47] In fact, we observed that *APOE* ε4 carriers showed lower mean scores on frontal/executive function tests than did noncarriers. However, our logistic regression analyses showed that the effects of severe WMHs on frontal/executive performance were strong even in *APOE* ε4 noncarriers. Moreover, the interaction effects of WMH severity and *APOE* ε4 on memory tests, and the lesser effect of WMH severity on memory impairment in *APOE* ε4 carriers, would rather support the notion that cognitive failures related to *APOE* ε4 and WMHs might arise from a distinct main disease process. Indeed, there are a few reports[14,20] that found no relation between the *APOE* ε4 allele and WMHs in dementia studies. Recent studies[44,48] also found an acceleration of memory decline; yet, similar acceleration of decline on any frontal/executive measure despite fibrillar amyloid deposits in the frontal regions of *APOE* ε4 carriers was not found.[44,48] It was suggested that modulation of activity in attention-control systems might be associated with elevated WMHs but not with amyloid burden.[30] On the other hand, amyloid burden, not white matter abnormalities, might be related to impaired default network activity related to memory function.[49]

There are several limitations to this study. First, the cross-sectional nature of the study did not allow us to find a change in the interactive effects between *APOE* and WMHs with disease progression. Second, the subjects in our study with severe WMHs might be a heterogeneous group, including individuals with subcortical ischemic vascular dementia and Alzheimer's disease with small vessel pathologies. However, it is possible that the cognitive phenotype reflected the severity of regional brain pathology rather than the type of pathology.[50] Third, we used our own 3-level WMH scale; however, the criteria for severe WMHs were similar to the brain imaging criteria for subcortical vascular dementia, Binswanger type, used by Erkinjuntti et al.[51] We also could not separately evaluate the periventricular white matter and

deep white matter hyperintensities that are assumed to be due to different mechanisms.[5,52] Fourth, there were restricted ranges in some cognitive test scores and ages, which could influence the findings (K-BNT score: 0–60; SVLT-delayed recall score: 0–12; RCFT-delayed recall score: 0–35; Digit Span Test-backward score: 0–8; Stroop Test-color reading score: 0–112; COWAT score: 0–30; age: 40–90 years). To minimize this effect, we used age-specific, gender-specific, and education-specific norms for each test based on reference standards to classify cognitively impaired individuals in multivariate logistic regression analyses. Another point is that, because of a very small number of cognitively normal individuals in this study, the study did not address whether WMHs affected cognition independently from dementia. However, the Clinical Dementia Rating score showed an upward trend as WMH severity increased (Mantel-Haenszel χ^2 test: $P < .001$) (see Table 1). Finally, we could not evaluate the effect of the *APOE* ε2 allele,[53] known to be associated with severe white matter disease, because of the relatively small frequency of this allele in our subjects.

In conclusion, severe WMHs appear to be predominantly associated with frontal/executive dysfunction, irrespective of the presence of the *APOE* ε4 allele. In addition, and more interestingly, WMH severity and *APOE* ε4 had an interactive effect on memory function, with WMH severity affecting memory impairment only in *APOE* ε4 noncarriers. These results support the potential value of further research examining the association between *APOE* genotype, WMHs, and cognitive impairment in the elderly.

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Additional information: The Clinical Research Center for Dementia of South Korea (CREDOS) database is owned by the Korean Ministry of Health and Welfare, Seoul, Republic of Korea. For information on accessing the database, contact Seong Hye Choi (seonghye@inha.ac.kr) or Seong Yoon Kim (seongyoonkim@gmail.com).
Supplementary material: Supplementary eTable 1 is available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Association Between White Matter Hyperintensity Severity and Cognitive Impairment According to the Presence of the Apolipoprotein E (*APOE*) ε4 Allele in the Elderly: Retrospective Analysis of Data From the CREDOS Study

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List of Supplementary Material for the article

1. **eTable 1** Effect of the *APOE* ε4 Allele on Cognitive Impairment

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Supplementary eTable 1. Effect of the *APOE* ε4 Allele on Cognitive Impairment

Function	Test	Model 1[a]		Model 2[b]	
		OR (95% CI)	*p*	OR (95% CI)	*p*
Language	K-BNT	1.29(1.14-1.46)	<.001	1.31(1.15-1.49)	<.001
Verbal memory	SVLT-delayed recall	2.47(2.15-2.83)	<.001	2.50(2.18-2.88)	<.001
Visuospatial memory	RCFT-delayed recall	2.30(2.01-2.63)	<.001	2.35(2.06-2.69)	<.001
Attention	Digit span-backward	1.17(1.03-1.33)	.016	1.20(1.06-1.36)	.005
Frontal/ executive Function	Stroop test-color reading	1.30(1.15-1.47)	<.001	1.35(1.19-1.53)	<.001
	COWAT	1.42(1.25-1.61)	<.001	1.48(1.30-1.68)	<.001

[a] Model 1: Adjusted by age, gender, education, illness duration, cerebrovascular risk factors (hypertension, diabetes, hyperlipidemia, cardiac disease), and depression score; [b] Model 2: Model 1+ Adjusted by white matter hyperintensities severity.

Abbreviation: K-BNT=Korean Boston Naming Test, SVLT=Seoul Verbal Learning Test, RCFT=Rey-Complex Figure Test, COWAT=Controlled Oral Word Association Test, OR=Odd Ratio; CI=Confidence Interval.