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Original Article

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Association Between Body Mass Index and Cognitive Function in Mild Cognitive Impairment Regardless of APOE ε4 Status

Ye Sol Mun,[1] **Hee Kyung Park**,[2,3] **Jihee Kim**,[2] **Jiyoung Yeom**,[2] **Geon Ha Kim**,[2] **Min Young Chun**,[4] **Hye Ah Lee**,[5] **Soo Jin Yoon**,[6] **Kyung Won Park**,[7] **Eun-Joo Kim**,[8] **Bora Yoon**,[9] **Jae-Won Jang**,[10] **Jin Yong Hong**,[11] **Seong Hye Choi**,[12] **Jee Hyang Jeong**[1]

[1]Department of Neurology, Ewha Womans University Seoul Hospital, Ewha Womans University College of Medicine, Seoul, Korea
[2]Department of Neurology, Ewha Womans University Mokdong Hospital, Ewha Womans University College of Medicine, Seoul, Korea
[3]Division of Psychiatry, Division of Mental Health Care of Older People, University College London, London, UK
[4]Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[5]Clinical Trial Center, Mokdong Hospital, Ewha Womans University College of Medicine, Seoul, Korea
[6]Department of Neurology, Eulji University School of Medicine, Daejeon, Korea
[7]Department of Neurology, Dong-A University College of Medicine, Busan, Korea
[8]Department of Neurology, Pusan National University School of Medicine, Busan, Korea
[9]Department of Neurology, Konyang University Hospital, College of Medicine, Konyang University, Daejeon, Korea
[10]Department of Neurology, Kangwon National University Hospital, Kangwon National University College of Medicine, Chuncheon, Korea
[11]Department of Neurology, Yonsei University Wonju College of Medicine, Wonju, Korea
[12]Department of Neurology, Inha University Hospital, Inha University School of Medicine, Incheon, Korea

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Correspondence to
Jee Hyang Jeong
Department of Neurology, Ewha Womans University Seoul Hospital, Ewha Womans University College of Medicine, 260, Gonghang-daero, Gangseo-gu, Seoul 07804, Korea.
Email: jjeong@ewha.ac.kr

Seong Hye Choi
Department of Neurology, Inha University Hospital, Inha University School of Medicine, 27, Inhang-ro, Jung-gu, Incheon 22332, Korea.
Email: seonghye@inha.ac.kr

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ORCID iDs
Ye Sol Mun
https://orcid.org/0000-0002-5067-8667
Hee Kyung Park
https://orcid.org/0000-0001-6339-0059
Jihee Kim
https://orcid.org/0000-0002-1047-2971
Jiyoung Yeom
https://orcid.org/0000-0001-6325-1008
Geon Ha Kim
https://orcid.org/0000-0001-5395-1924

ABSTRACT

Background and Purpose: In this study we aimed to find the association between neuropsychological performance and body mass index (BMI) in patients with mild cognitive impairment (MCI). In addition, we investigated the effects of the apolipoprotein E (APOE) genotype in the relationship between the BMI and cognition in MCI.
Methods: We enrolled a cohort of 3,038 subjects with MCI aged 65–90 from the Clinical Research Center for Dementia of South Korea and a dementia cohort of the Ewha Womans University Mokdong Hospital. MCI patients were classified into three subgroups according to the Asian standard of BMI. We compared cognitive performances between groups by one-way analysis of variance. To investigate the effects of the APOE genotype, we used multivariate linear regression models after adjusting for possible confounders.
Results: Even though normal BMI groups were younger, had more females, and had less comorbidities, the higher BMI groups had better cognitive functions. Among subjects with APOE ε4 carriers, there was a positive relationship between the BMI and the memory task alone.
Conclusions: Our findings suggested that higher BMI in patients with MCI were associated with better cognitive performance. The effects of the APOE ε4 genotype in the associations between BMI and cognition were distinguishing. Therefore, according to physical status, APOE ε4 genotype-specific strategies in the assessments and treatments may be necessary in elderly patients with MCI.

Keywords: Body Mass Index; Apolipoprotein E; Cognitive Function; Mild Cognitive Impairment

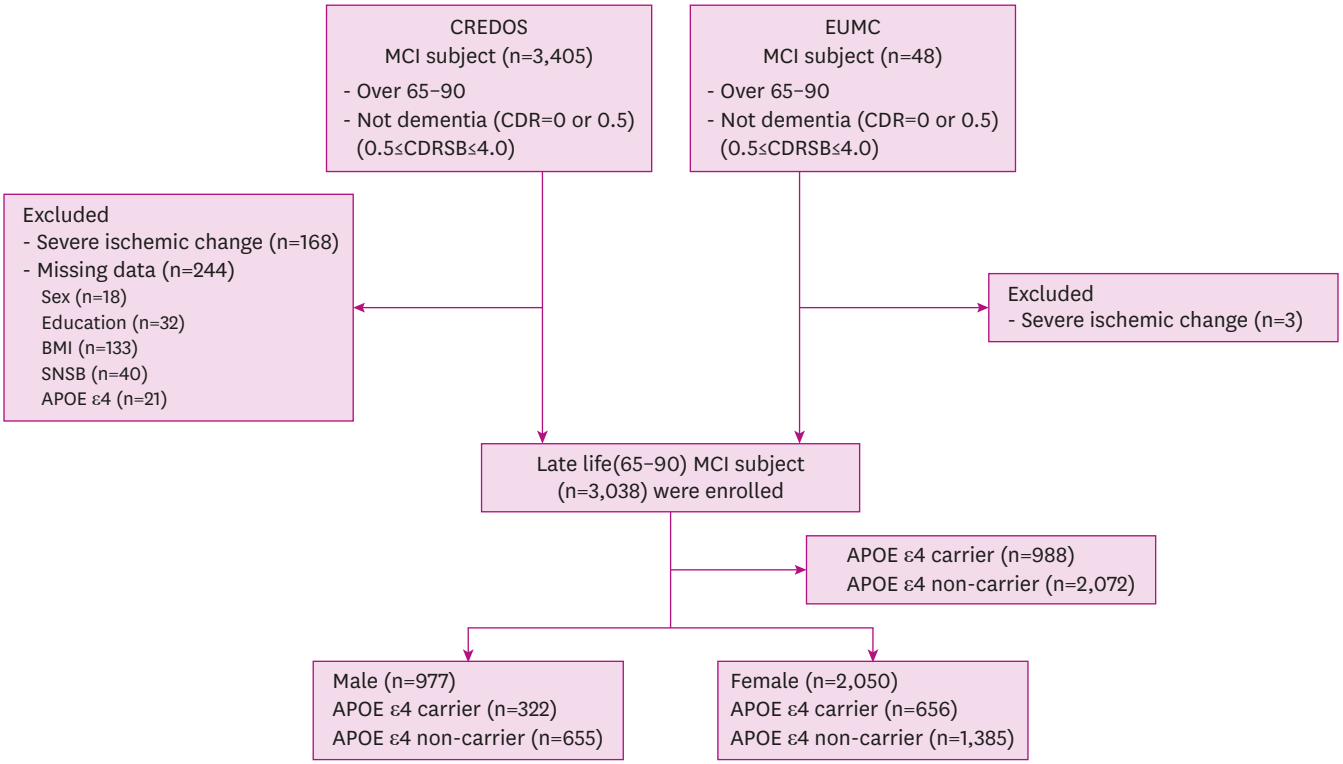

Fig. 1. Flow chart showing the process of selecting the study population.
CREDOS: Clinical Research Center for Dementia of South Korea, MCI: mild cognitive impairment, CDR: clinical dementia rating, CDRSB: clinical dementia rating sum of boxes, EUMC: Ewha Womans University Medical Center, BMI: body mass index, SNSB: Seoul Neuropsychological Screening Battery, APOE: apolipoprotein E.

1) cognitive impairment, especially subjective memory complaint by patients or caregivers, 2) evidence of objective memory or other cognitive function impairment in neuropsychological tests, lower than expected for the patient's age and educational level, 3) largely maintained activities of daily living and minimally impaired instrumental activity of daily living (IADL), and 4) absence of dementia in the individual.

Additionally, we included the Clinical Dementia Rating (CDR) and CDR sum of boxes (CDRSB) as inclusion criteria. The CDR score is 0 or 0.5, and the CDRSB should be in the range 0.5–4.0. Patients with a global CDR score of 0 were selected as those with a CDRSB of 0.5, because one or more cognitive domains were lowered to 1SD or less in an objective neuropsychological test. A CDR score of 0.5 indicates a decline in cognitive function, but the IADL remains within the normal range (<0.43). Subjects were excluded for the following reasons:

1) history of significant hearing or visual impairment rendering participation in the interview difficult, 2) history of following neurologic disorder(brain tumor, subarachnoid hemorrhage, epilepsy, encephalitis, and metabolic encephalopathy), 3) severe white matter hyperintensities that might be vascular rather than degenerative, 4) disorder of thyroid gland, syphilis, or vitamin B12 deficiency, 5) history of a psychiatric disorder, including schizophrenia, bipolar disorder, and major depressive disorder and other, 6) history of using psychoactive substances other than alcohol, 7) missing data, such as for sex, education, BMI, neuropsychological tests, and the APOE ε4 genotype.

Clinical evaluations

All participants were evaluated by means of comprehensive interviews, neurological tests, and laboratory results. We obtained the demographic data about the patients and caregivers, lifestyle and family history, and past medical history, including vascular risk factors, such as hypertension (HTN), hyperlipidemia (HL), diabetes mellitus (DM), cardiac disease, previous stroke history, and brain trauma. Laboratory tests included complete blood counts, chemistry, electrolytes, urinalysis, syphilis serology, thyroid function test, and vitamin B12/folate. We assessed APOE genotype by polymerase chain reaction.[25] We classified the APOE genotype into ε4 carrier and non-carrier according to the presence of the ε4 allele, and categorized the ε4 carrier group into homozygote and heterozygote. We also evaluated the severity of white-matter hyperintensities (WMH) using the T2 or fluid-attenuated inversion recovery axial images on brain magnetic resonance imaging. These two ratings were combined into three groups of WMH severity: minimal, moderate and severe.[26]

BMI

We calculated BMI as weight in kilograms divided by height in meters squared (kg/m^2). We classified all patients into four BMI subgroups (Less than 18.5 kg/m^2 = underweight, 18.5–23 kg/m^2 = normal, 23–25 kg/m^2 = overweight, and >25 kg/m^2 = obesity) based on the World Health Organization (WHO) guidelines for Asian populations.[27] Given that we had too few patients for the underweight group (n=128), we divided the subjects into three groups (normal, overweight, and obese) by combining the underweight and the normal-weight group.

Neuropsychological assessment

All subjects received a standardized neuropsychological battery, the Seoul Neuropsychological Screening Battery,[28] and only patients who received all the tests below were included in the analysis. We assessed global cognition using the Korean Mini-Mental State Examination (K-MMSE),[29] the CDR, and the CDRSB.[30] We used the Korean version of the Boston Naming Test (K-BNT),[31] the Rey-Osterrieth Complex Figure Test (RCFT), the Seoul Verbal Learning Test (SVLT), phonemic and semantic Controlled Oral Word Association Test (COWAT, phonemic/animal fluency), and the Stroop test to assess each cognitive domain. The raw score of the neuropsychological tests was used for the analysis.

Statistical analysis

We analyzed the frequencies and calculated the mean values of the clinical characteristics by the total sample (**Table 1**). We presented age, education, and BMI corresponding to continuous variables as mean and standard deviations. We presented sex, APOE ε4, CDR, comorbid conditions, and ischemic change corresponding to categorical variables as numbers and percentages. We conducted clinical comparisons between BMI categories using one-way analysis of variance for continuous variables and the chi-squared test for categorical variables. We examined differences between the three groups according to the BMI using analyses of the covariate, and applied a Bonferroni correction to the *post hoc* tests in neuropsychological measures (K-BNT, RCFT copy, SVLT/RCFT delay recall, animal/phonemic fluency, Stroop test, K-MMSE, CDRSB) performance among MCI patients, after adjusting for the covariates, including age, sex, education, HTN, HL, DM, cardiac disease, previous stroke, and APOE ε4. Last, we used multiple linear regression to investigate the association between various neuropsychological tests and BMI after adjusting for possible confounders, such as age, education, HTN, HL, DM, cardiac disease, and previous stroke; we did additional analysis of the effects of APOE genotype and sex, separately. Considering the influence of APOE ε4, we further analyzed it by dividing it into homozygote and heterozygote groups. We

Table 1. Demographics and clinical characteristics of mild cognitive impairment subjects

Variable	Total	Normal weight (BMI<23)	Overweight (23≤BMI<25)	Obese (BMI≥25)	*p*-value
No.	3,038	1,317 (43.4)	802 (26.4)	919 (30.3)	
Age (yr)	73.55±5.13	74.09±5.35	73.24±5.27	73.05±5.23	<0.001
Sex					
Female	2,041 (67.2)	885 (67.2)	514 (64.1)	642 (69.9)	0.039
Education (yr)	7.78 (5.44)	7.81 (5.38)	8.02 (5.56)	7.52 (5.42)	0.156
No education	529 (17.4)	212 (16.1)	144 (18.0)	173 (18.8)	
≤6 yr	1,037 (34.1)	466 (35.4)	251 (31.3)	320 (34.8)	
7–12 yr	916 (30.2)	405 (30.8)	240 (29.9)	271 (29.5)	
≥13 yr	556 (18.3)	234 (17.8)	167 (20.8)	155 (16.9)	
Family history					
Dementia	343 (11.3)	144 (21.2)	79 (18.9)	120 (24.1)	0.153
Stroke	300 (10.0)	124 (9.5)	68 (8.6)	108 (12.0)	0.190
APOE ε4					
APOE ε4(+)	988 (32.5)	464 (35.2)	242 (30.2)	282 (30.7)	0.020
BMI (kg/m^2)	23.66 (3.13)	20.94 (1.63)	24.01 (0.58)	27.27 (2.10)	<0.001
Comorbid conditions					
Hypertension	1,557 (51.3)	549 (41.8)	409 (51.1)	599 (65.3)	<0.001
Hyperlipidemia	639 (21.0)	213 (16.2)	172 (21.5)	254 (27.8)	<0.001
Diabetes mellitus	684 (22.5)	254 (19.3)	198 (24.8)	232 (25.4)	0.001
Cardiac disease	484 (15.9)	169 (12.9)	139 (17.4)	176 (19.3)	<0.001
Stroke	97 (3.2)	31 (2.4)	21 (2.6)	45 (4.9)	0.002
Brain trauma	78 (2.6)	36 (2.8)	18 (2.3)	24 (2.7)	0.788
CDR					
0	170 (5.6)	61 (4.6)	56 (7.0)	53 (5.8)	
0.5	2,868 (94.4)	1,256 (95.4)	746 (93.0)	866 (94.2)	0.071
Ischemic change					
Mild	2,631 (86.6)	1,150 (88.1)	691 (87.1)	790 (86.7)	0.591
Moderate	378 (12.4)	155 (11.9)	102 (12.9)	121 (13.3)	0.591

Data are shown as mean±standard deviation or number (%).
BMI: body mass index, APOE: apolipoprotein E, CDR: clinical dementia rating.

computed statistical data with SPSS, version 20.0 (IBM, Chicago, IL). We considered results statistically significant for $p<0.05$.

Ethics statement

All participants and their caregivers provided written informed consent, and the study protocol was approved by the Institutional Review Board (IRB) of Ewha Womans University Mokdong Hospital (IRB EUMC 2018-08-005).

RESULTS

The demographics of the 3,038 MCI patients are summarized in **Table 1**. The three BMI groups showed statistically significant differences in sex, age, APOE ε4, HTN, HL, DM, cardiac disease, and stroke. The normal-weight group had lower comorbidities, more females, and an older population than did the overweight and obese group. The APOE ε4 carriers in the overweight and the obesity groups accounted for about 30%, that in the normal-weight group about 35%.

When the APOE ε4 carriers and the non-carriers were compared, the APOE ε4 carrier group had significantly lower BMI than did the non-carriers (23.40 kg/m^2 vs 23.78 kg/m^2, $p=0.002$). The proportion of family history of dementia (13.6% vs 9.9%, $p=0.011$) and of HL (23.2% vs 19.7%, $p=0.027$) was more common in the APOE 4 carriers than in the non-carriers.

Comparisons of cognitive function between the three groups, adjusting for age, sex, education level, HTN, HL, DM, cardiac disease, previous stroke, and presence of APOE ε4, are presented in **Table 2**. There were significant differences between the three BMI groups in K-BNT, RCFT copy, SVLT delay recall, RCFT delay recall, animal fluency, phonemic fluency, Stroop test, MMSE, and CDRSB. The overweight group had higher scores in the K-BNT, RCFT delay recall, phonemic fluency, Stroop test, MMSE and CDRSB than did those in the normal weight group. The obese group performed better in the K-BNT, SVLT delay recall, RCFT delay recall, Stroop test and K-MMSE and had lower score in the CDRSB than did the normal-weight group.

To find the relationships between BMI, APOE genotype, sex, and cognitive function, we did a multiple regression analysis while controlling for extra variables. The results are presented in **Table 3**. As BMI increased, scores of all neurocognitive tests were significantly increased (RCFT copy, p=0.047; animal fluency, p=0.039; phonemic fluency, p=0.013; SVLT delay recall, p=0.005; RCFT delay recall, K-MMSE, p=0.001; K-BNT and Stroop test, p<0.001), and CDRSB (p=0.001) was decreased.

For the effect of the APOE genotype, in the APOE ε4 carrier group, there was a significant relationship only with memory tasks. As BMI increased in the APOE ε4 carriers, scores significantly increased in the SVLT delay recall (p=0.017) and RCFT delay recall (p=0.002) tasks. In the APOE ε4 non-carrier group, there was a significant positive association between BMI and K-BNT (p<0.001), animal fluency (p=0.022), phonemic fluency (p=0.018), Stroop test (p=0.002), and K-MMSE (p=0.002), but CDRSB (p=0.003) had a negative association with BMI. The linear regression showed that the BMI × APOE ε4 status interaction revealed significant differences only in memory. This result suggested that BMI affects the memory of APOE carriers as a modifying factor. The effect of sex was further analyzed, but we did not find the significant results we expected.

Table 2. Comparison of neuropsychological test performance between BMI subgroups

Cognitive function	Normal (BMI<23)	Overweight (23≤BMI<25)	Obese (BMI≥25)	p-value
No.	1,317	802	919	
Language				
K-BNT	36.78±0.27	37.94±0.33*,§	38.50±0.32$^{‡,‖}$	<0.001
Visuospatial function				
RCFT copy	27.05±0.20	27.48±0.26	27.60±0.25	0.185
Verbal memory				
SVLT delay recall	2.77±0.72	2.98±0.91	3.14±0.09$^{†,‖}$	0.005
Visual memory				
RCFT delay recall	7.10±0.16	7.78±0.21*,§	7.89±0.20$^{†,‖}$	0.004
Frontal/executive function				
Animal fluency	11.57±0.11	11.90±0.14	11.86±0.13	0.100
Phonemic fluency	16.57±0.26	17.88±0.33†,§	17.20±0.32	0.008
Stroop test	59.20±0.71	63.57±0.90‡,§	63.11±0.85$^{†,‖}$	<0.001
General index				
MMSE	23.82±0.10	24.17±0.12*,§	24.34±0.12$^{†,‖}$	0.002
CDRSB	1.76±0.03	1.64±0.04†,§	1.61±0.04$^{†,‖}$	0.001

Data are shown as adjusted mean±standard deviation.
SD: standard distribution, BMI: body mass index, K-BNT: Korean version of the Boston Naming Test, RCFT: Rey-Osterrieth Complex Figure Test, SVLT: Seoul Verbal Learning Test, MMSE: Mini-Mental State Examination, CDRSB: clinical dementia rating sum of boxes.
$^{*}p$<0.05, $^{†}p$<0.01, $^{‡}p$<0.001, adjusted by age, sex, years of education, hypertension, hyperlipidemia, diabetes mellitus, previous stroke, apolipoprotein E ε4 genotype; §Bonferroni's *post hoc* analyses comparing normal and overweight group; $^{‖}$Bonferroni's *post hoc* analyses comparing normal and obese group.

Table 3. Association between BMI and cognitive function according to APOE ε4 genotype

B (SE)	Total	APOE ε4 carrier	APOE ε4 non-carrier	*p*-value for BMI × APOE
Language				
K-BNT	0.259 (0.058)‡	0.088 (0.100)	0.336 (0.071)‡	0.388
Visuospatial function				
RCFT copy	0.091 (0.044)*	0.077 (0.080)	0.094 (0.053)	0.355
Verbal memory				
SVLT delay recall	0.044 (0.015)†	0.065 (0.027)*	0.031 (0.018)	0.018
Visual memory				
RCFT delay recall	0.114 (0.035)‡	0.185 (0.061)†	0.078 (0.043)	0.003
Frontal/executive function				
COWAT animal fluency	0.049 (0.023)*	0.003 (0.040)	0.069 (0.029)*	0.947
COWAT phonemic fluency	0.139 (0.058)*	0.083 (0.101)	0.166 (0.071)*	0.418
Stroop test	0.579 (0.156)‡	0.526 (0.287)	0.604 (0.186)‡	0.067
General index				
MMSE	0.074 (0.021)‡	0.059 (0.037)	0.082 (0.025)‡	0.117
CDRSB	−0.021 (0.006)‡	−0.015 (0.011)	−0.024 (0.007)‡	0.199

Multivariate linear regression analysis was performed after adjusting for age, education, hypertension, hyperlipidemia, diabetes mellitus, cardiac disease, previous stroke.
SE: standard error, BMI: body mass index, APOE: apolipoprotein E, K-BNT: Korean version of the Boston Naming Test, RCFT: Rey-Osterrieth Complex Figure Test, SVLT: Seoul Verbal Learning Test, COWAT: Controlled Oral Word Association Test, MMSE: Mini-Mental State Examination, CDRSB: clinical dementia rating sum of boxes.
*$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$.

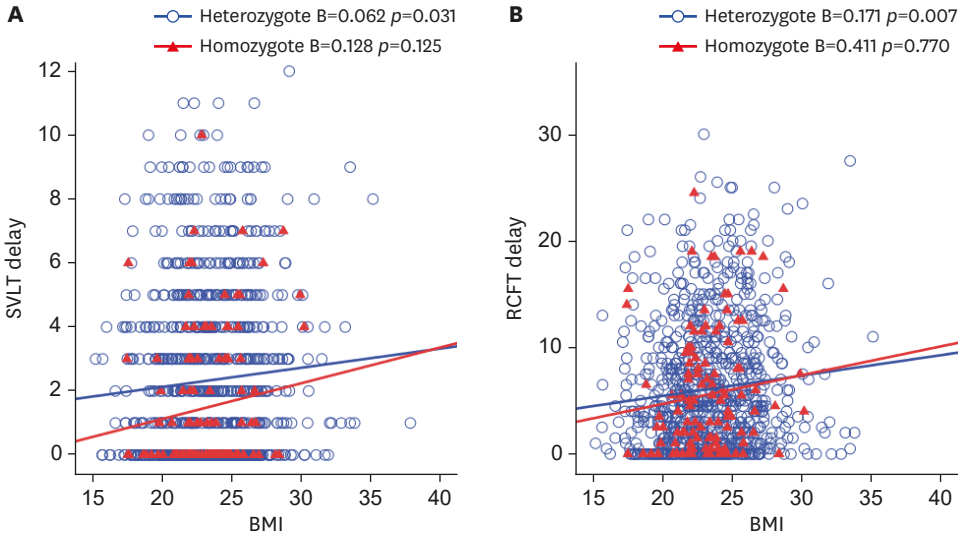

Fig. 2. Regression analysis for the association of BMI and memory test among apolipoprotein E ε4 heterozygote and homozygote groups. (A, B), values of the X axis represent BMI (kg/m²) and values of the Y axis represent SVLT delay and RCFT delay, respectively.
BMI: body mass index, SVLT: Seoul Verbal Learning Test, RCFT: Rey-Osterrieth Complex Figure Test.

Next, we analyzed the association between homozygote (n=123) and heterozygote (n=865) in the APOE ε4 carrier group (**Fig. 2**). Positive associations between BMI and verbal memory (p=0.031) and visual memory (p=0.007) were significant only in the heterozygote group.

DISCUSSION

In this study we report relationships between BMI and cognitive function with modifying effects of APOE ε4 genotype and sex. First, higher BMI was associated with better cognitive

functions in late-life MCI patients. Second, in the APOE ε4 carriers, there was a positive association only between the BMI and the memory task, and performance in memory was improved as BMI increased, but a sex difference was not observed. Specifically, a significant association between the APOE ε4 gene and memory was found only in the heterozygote group. Conversely, cognitive functions (language, frontal function, and general index) excluding memory were improved as BMI increased in the APOE ε4 non-carrier group

We found that neuropsychological test performance is improved as BMI increases in MCI patients. This corresponds with previous studies' demonstration that in MCI patients, the overweight and obese had less risk of cognitive decline than did those with normal BMI.[32,33] The underweight MCI group had an increased risk for progression to AD[34,35] in longitudinal follow-up studies. Furthermore, patients with low BMI correlated with structural alterations, including more advanced medial temporal atrophy and more microbleeds.[36] In contrast to people with low BMI, normal older adults with high BMI had a better cognitive function, a slow rate of cognitive decline, and a decreased risk of developing dementia.[5,8,37] Our finding suggested that a high BMI index is a predictor of cognitive function and good health status in late life, as evidenced by the "obesity paradox."

We also found that APOE ε4 carriers were associated with only memory tests, because BMI increased regardless of sex. Not surprisingly, a significant positive relationship between BMI and memory was found only in the APOE ε4 heterozygote group. These results were consistent with some previous studies. Overweight and obese patients performed better on memory recall tasks than did the underweight.[33] Moreover, in one longitudinal study, those in their 50s who had significantly decreased memory scores over the next decade were associated with weight loss, and this trend was more pronounced among the underweight.[38] The obese APOE ε4 carriers had a higher cognitive function score at baseline and less cognitive decline over time than did the underweight group.[39] Another study found that cognitive decline was less pronounced in the obese APOE ε4 groups than in those with normal BMI[33] The longitudinal study also demonstrated that low BMI was a risk factor for cognitive decline and dementia progression only in APOE carriers.[40]

Expanding upon these previous studies, our study has suggested that BMI is a significant modefying factor for the risk of dementia, even allowing for the APOE ε4 gene effect in MCI. The pathophysiological mechanism by which BMI triggers cognitive alteration has not yet been fully elucidated. Low body weight may be associated with poor intake of nutrition and with metabolic disturbances. The accumulation of Aβ in the APOE ε4 transporter is regulated by leptin signaling in the hypothalamus and promotes weight loss.[39] High BMI, reflecting healthy nutritional status,[41] associated with higher levels of leptin and adiponectin, may bring about oxidative damage to the neuronal cell membrane and facilitate hippocampal synaptic plasticity and improved cognitive function.[42-44] Healthy lifestyle prevented cognitive decline and diminished the risk of AD even given the effect of APOE ε4.[45-47] Therefore, high BMI in older MCI patients can indicate a healthy physical condition. It seems essential to maintain healthy body weight to stably preserve cognitive function in patients.

On the other hand, the positive association between BMI and verbal/visual memory was found only in the heterozygote group. Generally, having one ε4 allele increases the risk of developing AD three times, and having two ε4 alleles is twelve times more likely to develop AD than are non-carriers[48] and accelerates the age of onset.[49] The APOE ε4 homozygote carriers showed more severe memory loss than did the heterozygote group.[50,51] These results

indicate that the genetic influence of APOE ε4/ε4 is strong, and environmental factors as a protective factor have insignificant effects on individual cognitive function and dementia risk. Hence specific intervention is required according to the APOE ε4 subtype.

Last, we found no sex difference in the effect of BMI and APOE status on cognitive function, despite distinct effects of the APOE according to sex. One study revealed that increased BMI was associated with diminished cognitive function in males but not in females,[52] whereas Hayes et al.[12] found no sex difference in the association. This finding requires further study and confirmation, because sex-dependent relationships in the risk of developing AD and cognitive decrease according to APOE ε4 have shown conflicting results.

There are some limitations to this study. First, BMI is a proxy to measure an individual's obesity; in order to measure obesity precisely, variables such as waist circumference, percent body fat, and lean muscle mass should be included. Second, we did not use cerebrospinal fluid analysis, amyloid PET imaging, or other pathological studies to established AD pathology in this study. However, MCI was defined by the clinical criteria as well as by comprehensive neuropsychological test batteries. Some previous studies have reported that cognitive function declines when the BMI is lower than 18.5 kg/m^2 or higher than 30 kg/m^2. However, the same results were not obtained in this study (**Supplementary Table 1**), because the data for this study did not consider the sample size of the BMI subgroup. Also, Asians follow the BMI standards of the WHO-Westen Pacific Regional Office (WHO-WPRO) and are classified as overweight or obese differently from Westerners; So, there are not many elderly people with severely obese BMI over 30 in Korea. Therefore, further research on the difference between the underweight and severely obese groups is needed to show how high an individual's BMI is appropriate. In addition, longitudinal changes should be looked at together to clarify their causal relationship.

In conclusion, we investigated the association between BMI and comprehensive neuropsychological test batteries using a large sample of as an older MCI patients. The results highlight the importance of high BMI, which as a marker of good physical status may indicate improved cognitive function, and furthermore distinguished a subgroup of APOE ε4 allele carriers associated with BMI and cognition. Therefore, physical status and APOE ε4 genotype-specific strategies in the assessments and treatments may be necessary for elderly patients with MCI.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Comparison of neuropsychological test performance between BMI subgroups

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