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ORIGINAL ARTICLE

Effects of metabolic syndrome, apolipoprotein E, and CYP46 on cognition among Taiwanese Chinese

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Abstract The combined effects of metabolic syndrome and the apolipoprotein E and CYP46 genotypes on the risk of cognitive decline has yet to be determined among Taiwanese Chinese. Two hundred and nine mentally healthy middle-aged and older adults were assessed for metabolic syndrome, cognitive function using the Cognitive Abilities Screening Instrument, Mini-Mental State Examination, ApoE, and CYP46 polymorphisms. There were no differences in cognitive performance, ApoE epsilon4 (ε4) carrier status, or CYP46 genotypes between participants with and those without metabolic syndrome. The ε4 carriers and participants with the AA allele of CYP46 had significantly lower mental manipulation score. Metabolic syndrome and ε4 had synergistic effects on cognitive decline. Therefore, the ε4 carriers and participants with the AA allele of CYP46 have decreased mental manipulation ability. The metabolic syndrome may play a role in subtle cognitive dysfunction in ε4 carriers among Taiwanese Chinese.

Conflicts of interest: All authors have no conflicts of interest to declare.

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Introduction

There is currently a great deal of interest in the prevention of cognitive decline in the rapidly aging population. Ideally, preventive strategies require the identification of a suitable intervention approach. Alzheimer's disease (AD) is the most common cause of aged-related dementia [1,2]. Vascular risk factors such as hypertension, diabetes, and dyslipidemia may reduce cerebral perfusion, increase oxidative stress, or activate a neuroinflammatory response, all of which can trigger amyloid production [3] which is a pathological hallmark of AD. Metabolic syndrome is a clustering of cardiovascular and metabolic risk factors that increases the risk of developing atherosclerotic cardiovascular disease and stroke [4,5]. Previous studies have suggested that several of the individual components of metabolic syndrome are associated with cognitive impairment [6,7]. Nonetheless, although many studies suggest that the combined effects of metabolic syndrome-associated vascular risk factor may lead to a greater risk of cognitive decline, a growing number of reports have conflicting results [8,9].

The apolipoprotein E gene (ApoE), localized on chromosome 19, encodes cholesterol and other lipid transporters [10]. It is produced abundantly in the brain, where it appears to modulate neuritic growth [11], neuronal repair, and the development of senile plaque, vascular amyloid, and neurofibrillary tangle [12], which are all considered significant in the pathogenesis of AD. Although the distribution of ApoE alleles shows a wide variation across ethnic groups, several studies have demonstrated a relationship between ApoE $\varepsilon 4$ and increased risk of cognitive decline and dementia [13,14]. Furthermore, a growing body of evidence supports the association between ApoE polymorphisms, the early development of atherosclerosis, and cardiovascular events [12]. Other studies also report an association between ApoE polymorphisms and metabolic syndrome [15]. However, whether or not the combined effect of $\varepsilon 4$ and metabolic syndrome increases the risk of cognitive decline remains controversial [8,16].

The brain is the most cholesterol-rich organ in the body and cholesterol metabolism has been implicated in the pathogenesis of AD [17] through the accumulation of toxic peptide β-amyloid. However, there is still no consensus regarding the effect of cholesterol on cognitive decline or dementia [18]. Cholesterol 24S hydroxylase (CYP46) is encoded by the CYP46 gene, which is located in chromosome 14 and expressed exclusively in the brain [19]. Serum cholesterol is almost completely unable to pass through the blood—brain barrier so brain cholesterol is synthesized locally [20]. CYP46 regulates the elimination of excess cholesterol from the brain into the periphery [21] and lower CYP46 levels may lead to higher levels of brain cholesterol, thereby affecting its homeostasis. This, in turn, may also be involved in the pathogenesis of AD [22]. Recent studies support a genetic association between the intron 2 polymorphism of the CYP46 gene and the risk of AD [21,23], although other studies have not found this association [24].

The present study aimed to investigate the influence of the metabolic syndrome and lipid-related genes (ApoE and CYP46) on cognition and determine whether metabolic syndrome and genotypes of ApoE and CYP46 have a synergistic effect on cognitive decline among Taiwanese Chinese.

Methods

Participants

Two hundred and nine healthy middle-aged and older adults (age range, 56—81 years; 47% male; Taiwan Chinese ethnicity) were recruited from among individuals undergoing regular health examinations at Kaohsiung Medical University Hospital, Kaohsiung, Taiwan and in a community-based setting. The participants received a comprehensive medical evaluation including demographic data, history, physical examination, blood chemistry, and cognitive assessment. Resting blood pressure and fasting lipid and glucose levels were determined. Waist circumference was measured at the level of the iliac crest at minimal inspiration to the closest 0.1 cm. Individuals with a previous history or clinical evidence of neurologic (e.g., stroke, epilepsy, Parkinson's disease, dementia, traumatic brain injury, multiple sclerosis, brain tumor) or psychiatric (e.g., schizophrenia, affective disorders, substance abuse) diseases, and those with scores on the Cognitive Abilities Screening Instrument (CASI) [25] below a cut-off value adjusted by age and educational level were excluded. All of the participants were assessed for characteristics of metabolic syndrome and ApoE and CYP46 polymorphisms after providing informed consent.

Cognitive assessment

The participants' cognitive abilities were assessed using a Chinese version of the CASI [25], conducted by research assistants. The CASI included a 25-item test divided into nine cognitive domains of attention, mental manipulation, orientation, short-term memory, long-term memory, language ability, constructional praxis, category fluency, and abstraction and judgment. The maximum score was 100, with higher scores indicating better ability. For each participant, the total CASI score and the nine domain scores were calculated. Some of the CASI items are comparable to items used in the Mini-Mental State Examination (MMSE). Thus, a CASI-estimated MMSE score (MMSE-CE) [25] was also calculated.

Metabolic syndrome

Metabolic syndrome was defined using the modified version of the criteria introduced by the National Cholesterol Education Program - Adult Treatment Program III (NAEP-ATPIII) [26] as the presence of three or more of the following: fasting plasma glucose level $\geq$ 110 mg/dL or drug treatment for elevated glucose level; serum triglyceride level $\geq$ 150 mg/dL; serum high-density lipoprotein cholesterol (HDL-C) level $<$ 40 mg/dL for men and $<$50 mg/dL for women; blood pressure $\geq$ 130/85 mmHg or antihypertensive medication use; and a waist circumference $>$ 90 cm for men or $>$ 80 cm for women [27].

Apolipoprotein E genotyping

Genomic DNA was extracted from peripheral blood leukocytes using a QIAmp blood kit (QIAGEN). Exon 4 of the ApoE gene was amplified by polymerase chain reaction (PCR) with an upstream primer, 5′-TCGCGGGCCCCCGGGCCTGGTACA-3′ and a downstream primer, 5′- ACAGAATTCGCCCCGGCCTGGTACACTGCCA-3′ [28]. The PCR products were digested with HhaI and the fragments were separated by electrophoresis on a 6% polyacrylamide gel, followed by ethidium bromide staining. The DNA fragments were visualized by UV illumination. The ApoE genotypes were determined in a blinded fashion by scoring for a unique combination of fragment sizes, as described by Wenham et al. [28]. Allele frequencies were estimated by counting the alleles and calculating sample proportions.

CYP46 genotype

Genomic DNA was extracted from whole blood samples using a standard procedure. Information on single-nucleotide polymorphisms (SNP) involved in this study can be found in a public database (http://www.hapmap.org, ID rs754203). Genotypes were determined by real-time PCR and confirmed by DNA sequencing. The rs754203 was located on an A to G SNP in intron 2 of the CYP46 gene. For this SNP, the forward primer was 5′-GGGACAATCAAA-GAAGGAG-3′ and the reverse primer was 5′-AACCAAAGT-GACCCGAAG- 3′. The PCR product was digested with MspI. The CYP46 G allele generated two fragments of 114 bp, whereas the CYP46 A allele resulted in an uncut fragment of 254 bp.

Statistical analysis

Analysis of variance (ANOVA) and Chi-square test were used to compare the characteristics of demographic data and measurements of cognitive assessment between participants with and those without metabolic syndrome or ε4 and CYP46 genotypes. The effects of the interaction between metabolic syndrome, ε4 and CYP46 genotypes on cognitive measurements were evaluated by two-way analysis of covariance (ANCOVA), with age, sex, and educational level as covariates. Statistical significance was set at $p < 0.05$.

Results

When the participants were stratified according to the presence of metabolic syndrome, there were no differences in demographic characteristics, MMSE-CE scores, CASI total scores, all CASI sub-scores, or the percentages of ε4 carriers and CYP46 genotypes (Table 1).

The demographic characteristics, MMSE-CE scores, CASI scores, percentages of metabolic syndrome, and CYP46 genotypes were compared according to the presence or absence of the ε4 allele, with carriers and noncarriers revealing similar values for most items (Table 2). However, the ε4 carriers had a significantly decreased mean score of mental manipulation compared with nonε4 carriers (8.32 ± 1.63 vs. 8.87 ± 1.28), but there was no significant difference in the CASI total score between the two groups.

When the participants were stratified according to CYP46 genotypes, there was a significantly lower score of mental manipulation in participants with the AA CYP46 genotype compared with those with the AG/GG CYP46 genotypes (8.09 ± 1.64 vs. 8.61 ± 1.53; Table 3). There were no significant differences in demographic characteristics, MMSE-CE scores, CASI total scores, components of metabolic syndrome, or percentages of metabolic syndrome and ε4 carriers between the two groups (Table 3).

The statistical results using ANCOVA with age, sex, and educational level as covariates for the interactive effects of metabolic syndrome and the presence of ε4 and CYP46 genotypes as measures of cognition are summarized in Tables 4 and 5. There was a significantly combined effect in mental manipulation score and a marginal effect in the CASI total score between the metabolic syndrome and ε4 carriers. However, there was no interactive effect of metabolic syndrome and CYP46 polymorphism on CASI and MMSE-CE scores.

Discussion

The present study has several main findings. Firstly, there is no association between metabolic syndrome and cognitive performance by CASI score. Secondly, the ε4 carriers and

Table 1 Characteristics of participants by presence of metabolic syndrome.

	MeSy $n = 65$	NonMeSy $n = 144$	p
Ages (y)[a]	68.62 ± 7.16	67.53 ± 6.63	0.3037
Sex (M/F)[b]	30/35	75/69	0.4274
Education (y)[a]	10.58 ± 3.74	11.29 ± 3.97	0.2151
MMSE (score)[a]	25.97 ± 2.47	26.26 ± 2.37	0.4313
CASI-T (score)[a]	90.09 ± 4.74	90.53 ± 4.50	0.5334
ATT (score)	6.83 ± 1.10	7.10 ± 0.95	0.0853
MENMA (score)	8.38 ± 1.47	8.41 ± 1.66	0.9126
ORI (score)	17.65 ± 0.67	17.77 ± 0.93	0.2745
STM (no.)	9.06 ± 2.07	9.22 ± 1.78	0.5841
LTM (no.)	10.00 ± 0.00	10.01 ± 0.19	0.6563
LAN (no.)	9.74 ± 0.49	9.66 ± 0.55	0.2893
DRA (score)	9.80 ± 1.02	9.85 ± 0.86	0.7460
FLU(no.)	7.66 ± 2.10	7.46 ± 1.89	0.5058
A&J (score)	10.54 ± 1.62	10.73 ± 0.97	0.2196
ApoE ε4+, *n* (%)[b]	9 (13.85)	22 (15.28)	0.7875
CYP46, *n* (%)[b]			
AA	27 (41.54)	58 (40.28)	0.8636
AG/GG	38 (58.46)	86 (59.72)	

A&J = abstraction and judgment; APOE = apolipoprotein E; ATT = attention; CASI = cognitive abilities screening instrument; CYP46 = 24S-cholesterol hydroxylase; DRA = constructional praxis; F = female; FLU = category fluency; LAN = language ability; LTM = long-term memory; M = male; MENMA = mental manipulation; MeSy = metabolic syndrome; MMSE = Mini-Mental State Examination; ORI = orientation; STM = short-term memory.

[a] By analysis of variance (ANOVA).

[b] By Chi-square test.

Table 2 Characteristics of participants by presence of apolipoprotein E ε4.

	ε4+ $n = 31$	ε4− $n = 178$	p
Ages (y)[a]	66.74 ± 5.58	68.07 ± 6.99	0.2469
Sex (M/F)[b]	15/16	90/88	0.8232
Education (y)[a]	11.21 ± 3.59	11.04 ± 3.97	0.8133
MMSE (score)[a]	26.81 ± 2.20	26.06 ± 2.42	0.0912
CASI-T (score)[a]	91.03 ± 4.56	90.28 ± 4.58	0.4027
ATT (score)	7.13 ± 1.02	7.00 ± 1.01	0.5202
MENMA (score)	8.32 ± 1.63	8.87 ± 1.28	0.0401
ORI (score)	17.74 ± 0.51	17.73 ± 0.91	0.9197
STM (no.)	9.11 ± 2.02	9.18 ± 1.85	0.8551
LTM (no.)	10.00 ± 0.00	10.0 1 ± 0.17	0.6560
LAN (no.)	9.71 ± 0.57	9.68 ± 0.53	0.7897
DRA (score)	9.71 ± 1.30	9.85 ± 0.83	0.5533
FLU(no.)	7.45 ± 2.29	7.53 ± 1.90	0.8515
A&J (score)	10.81 ± 0.91	10.65 ± 1.02	0.3785
MeSy, *n* (%)[b]	9 (29.03)	56 (31.46)	0.7875
CYP46, *n* (%)[b]			
AA	12 (38.71)	73 (41.01)	0.8097
AG/GG	19 (61.29)	105 (58.99)	

A&J = abstraction and judgment; APOE = apolipoprotein E; ATT = attention; CASI = cognitive abilities screening instrument; CYP46 = 24S-cholesterol hydroxylase; DRA = constructional praxis; F = female; FLU = category fluency; LAN = language ability; LTM = long-term memory; M = male; MENMA = mental manipulation; MeSy = metabolic syndrome; MMSE = Mini-Mental State Examination; ORI = orientation; STM = short-term memory.
[a] By analysis of variance (ANOVA).
[b] By Chi-square test.

participants with the AA allele of CYP46 have significantly lower mental manipulation scores, although there are no significant differences in the CASI total and MMSE scores. Thirdly, there is a synergistic effect of the metabolic syndrome and ε4 on subtle cognitive dysfunction. As regards the neuro-psychological tests, the MMSE, although used most commonly in community-based epidemiologic studies [29], is limited in its ability to discriminate cognitive decline in nondemented participants. However, the CASI total score can be used as a summary index of basic cognitive skills and is useful for detecting dementia and mild cognitive impairment [25].

The diversity in study populations in terms of age and ethnicity, severity of individual components, time of exposure, and the use of medications may explain these variations. However, a more complex association is also likely. The lack of a clear definition of metabolic syndrome is due to an unclear pathogenesis [30] and this is another limitation. Further studies with long-term follow-up and serial assessments of metabolic syndrome are needed to further clarify the relationships found here.

The significantly lower mental manipulation score of the ε4 carriers is not surprising because the CASI total scores did not show a difference in participants with or without ε4. This finding is in line with a previous study using cognitive event-related potentials [8]. Neuroimaging studies using positron emission tomography and functional magnetic resonance imaging (MRI) also support the association of the ε4 allele with functional brain abnormalities in participants with intact cognition [31,32].

However, there are still discrepancies in the literature regarding the impact of ApoE ε4 on cognitive decline in normal adults [14]. One reason for this discrepancy is that genetic effects on cognition are complex, with a possible involvement of several genes and a synergistic interaction with environmental factors [14]. Other explanations include age, ethnicity, sample size, and variability of the testing instruments. Cognition involves several domains and recent reports demonstrate that ApoE ε4 has rather specific and small adverse effects on cognitive performance [14]. Various neuro-psychological tests have been used as an index of cognitive function. However, these are also limited by "floor or ceiling" effects, which involve limited sensitivity in very mildly impaired participants.

There is a significant combined effect in mental manipulation score and a marginal effect in the CASI total score between metabolic syndrome and ε4 carriers in the present study. Dyslipidemia is a critical diagnostic component of metabolic syndrome [33]. Various ApoE genotypes have different effects on cholesterol metabolism and can influence the risk of cognitive decline through fluctuations in brain cholesterol homeostasis [12]. Most studies support the association of hypertension and diabetes with increased risk of cognitive decline and dementia [34].

Moreover, a previous study suggests that the impact of metabolic syndrome or individual components of metabolic syndrome on structural MRI of the brain differs according to

Table 3 Characteristics of participants by presence of CYP46 genotypes.

	AA ($n = 85$)	AG/GG ($n = 124$)	p
Ages (y)[a]	67.82 ± 7.14	67.90 ± 6.59	0.9349
Sex (M/F)[b]	41/44	64/60	0.6314
Education (y)[a]	10.88 ± 3.93	11.19 ± 3.90	0.5753
MMSE (score)[a]	25.88 ± 2.38	26.36 ± 2.40	0.1550
CASI-T (score)[a]	89.92 ± 4.57	90.72 ± 4.56	0.2151
ATT (score)	7.05 ± 1.10	7.00 ± 0.94	0.7484
MENMA (score)	8.09 ± 1.64	8.61 ± 1.53	0.0226
ORI (score)	17.64 ± 1.00	17.79 ± 0.75	0.2618
STM (no.)	9.22 ± 1.79	9.14 ± 1.94	0.7473
LTM (no.)	9.99 ± 0.11	10.02 ± 0.18	0.1639
LAN (no.)	9.70 ± 0.49	9.67 ± 0.56	0.6099
DRA (score)	9.89 ± 0.79	9.79 ± 0.99	0.4007
FLU(no.)	7.36 ± 1.94	7.63 ± 1.96	0.3373
A&J (score)	10.64 ± 0.97	10.69 ± 1.02	0.6776
MeSy, *n* (%)[b]	27 (31.76)	38(30.65)	0.8636
ApoE ε4+, *n* (%)[b]	12 (14.12)	19(15.32)	0.8097

A&J = abstraction and judgment; APOE = apolipoprotein E; ATT = attention; CASI = Cognitive Abilities Screening Instrument; CYP46 = 24S-cholesterol hydroxylase; DRA = constructional praxis; F = female; FLU = category fluency; LAN = language ability; LTM = long-term memory; M = male; MENMA = mental manipulation; MeSy, metabolic syndrome; MMSE = Mini-Mental State Examination; ORI = orientation; STM = short-term memory.
[a] By analysis of variance (ANOVA).
[b] By Chi-square test.

Table 4 Characteristics of participants by presence of metabolic syndrome and apolipoprotein E ε4.

	Metabolic syndrome		Nonmetabolic syndrome		*p*		
ApoE	ε4+ (n = 9)	ε4− (n = 56)	ε4+ (n = 22)	ε4− (n = 122)	MeSy	ε4	MeSy[a]ε4
MMSE (score)	25.78 ± 2.39	26.00 ± 2.50	27.23 ± 2.02	26.08 ± 2.39	0.1720	0.5294	0.1452
CASI-T (score)	88.86 ± 5.70	90.40 ± 4.57	92.05 ± 3.70	90.25 ± 4.60	0.1039	0.7692	0.0505
ATT (score)	6.78 ± 0.97	6.84 ± 1.12	7.27 ± 1.03	7.07 ± 0.94	0.1850	0.9131	0.5823
MENMA (score)	8.00 ± 1.41	8.45 ± 1.48	9.23 ± 1.07	8.26 ± 1.70	0.2093	0.4418	0.0484
ORI (score)	17.67 ± 0.50	17.64 ± 0.70	17.77 ± 0.53	17.77 ± 0.99	0.5287	0.9052	0.9372
STM (no.)	8.28 ± 3.04	9.19 ± 1.87	9.45 ± 1.37	9.18 ± 1.85	0.2463	0.2630	0.1299
LTM (no.)	10.00 ± 0.00	10.00 ± 0.00	10.00 ± 0.00	10.01 ± 0.20	0.9261	0.7994	0.9410
LAN (no.)	9.89 ± 0.22	9.71 ± 0.51	9.63 ± 0.65	9.66 ± 0.53	0.0981	0.6599	0.3431
DRA (score)	9.22 ± 2.33	9.89 ± 0.59	9.91 ± 0.43	9.84 ± 0.92	0.1167	0.1024	0.0534
FLU(no.)	6.78 ± 2.54	7.80 ± 2.01	7.73 ± 2.19	7.41 ± 1.84	0.9048	0.4218	0.1751
A&J (score)	10.56 ± 0.73	10.54 ± 1.11	10.91 ± 0.97	10.70 ± 0.97	0.3532	0.6248	0.7267

A&J = abstraction and judgment; APOE = apolipoprotein E; ATT = attention; CASI = Cognitive Abilities Screening Instrument; DRA = constructional praxis; F = female; FLU = category fluency; LAN = language ability; LTM = Long-Term Memory; M = male; MENMA = mental manipulation; MeSy = metabolic syndrome; MMSE = Mini-Mental State Examination; ORI = orientation; STM = short-term memory.

[a] 2-way analysis of covariance (ANCOVA) with age, sex, and educational level as covariate.

the ApoE genotype [35]. To complicate matters, possession of one or more ε4 alleles further increases the risk of dementia. Therefore, although this study implies that metabolic syndrome may play a role in subtle cognitive dysfunction in the presence of the ApoE ε4 allele among Taiwanese Chinese, large-scale and cohort studies are still necessary to further confirm such an interaction.

The present study shows that participants with the AA allele of CYP46 have significantly lower mental manipulation scores and that there is no interactive effect between metabolic syndrome and CYP46 genotypes on cognition. Previous studies have reported that CYP46 polymorphism is associated with an increased β-amyloid load in the brain [36] and is a genetic risk for AD [21,23] via cholesterol metabolism. Findings of a longitudinal study suggest that CYP46 genotypes may play a role in modulating the course of cognitive decline in later life [23]. A neuroimaging study also supported the association of the CYP46 AA allele with the severity of white matter lesions in individuals with mild cognitive impairment [37].

However, an increasing body of evidence suggests a link between cholesterol turnover and AD [24]. Moreover, despite advances in research on the pathogenesis and risk factors that predispose to AD and cognitive decline, many key aspects remain unclear. At present, the relationship among cholesterol levels, CYP46 polymorphisms, and cognition is less understood [3,24]. The inconsistent results are mainly attributable to the effect of gene—gene and gene—environmental interactions. Furthermore, the polygenic nature of metabolic syndrome and the related cardiovascular risk factors suggest that a single gene is unlikely to be responsible for the development of cognitive decline

Table 5 Characteristics of participants by presence of metabolic syndrome and CYP46 genotypes.

	Metabolic syndrome		Nonmetabolic syndrome		*p*		
CYP46	AA (n = 27)	AG/GG (n = 38)	AA (n = 58)	AA/AG (n = 86)	MeSy	CYP	MeSy[a]CYP
MMSE (score)	25.93 ± 2.04	26.00 ± 2.76	25.86 ± 2.54	26.52 ± 2.22	0.5287	0.3137	0.4209
CASI-T (score)	90.37 ± 3.80	89.89 ± 5.34	89.71 ± 4.91	91.08 ± 4.15	0.8047	0.4037	0.4988
ATT (score)	6.81 ± 1.21	6.84 ± 1.03	7.16 ± 1.04	7.07 ± 0.90	0.1274	0.9392	0.2212
MENMA (score)	8.33 ± 1.47	8.42 ± 1.48	7.98 ± 1.72	8.70 ± 1.56	0.6926	0.0922	0.2880
ORI (score)	17.52 ± 0.85	17.74 ± 0.50	17.71 ± 1.06	17.81 ± 0.83	0.3064	0.2296	0.7185
STM (no.)	9.46 ± 1.54	8.78 ± 2.35	9.11 ± 1.89	9.30 ± 1.71	0.9492	0.4338	0.3153
LTM (no.)	10.00 ± 0.00	10.00 ± 0.00	9.98 ± 0.13	10.02 ± 0.22	0.9354	0.3420	0.5002
LAN (no.)	9.79 ± 0.37	9.70 ± 0.56	9.67 ± 0.53	9.65 ± 0.57	0.1730	0.6370	0.9436
DRA (score)	10.00 ± 0.00	9.66 ± 1.32	9.84 ± 0.95	9.85 ± 0.80	0.9431	0.2527	0.2682
FLU(no.)	7.48 ± 1.95	1.79 ± 2.22	7.31 ± 1.96	7.56 ± 1.84	0.2550	0.3702	0.6764
A&J (score)	10.74 ± 1.02	10.39 ± 1.08	10.59 ± 0.96	10.83 ± 0.97	0.4865	0.7373	0.0970

A&J = abstraction and judgment; ATT = attention; CASI = Cognitive Abilities Screening Instrument; CYP46 = 24S-cholesterol hydroxylase; DRA = constructional praxis; F = female; FLU = category fluency; LAN = language ability; LTM = long-term memory; M = male; MENMA = mental manipulation; MeSy = metabolic syndrome; MMSE = Mini-Mental State Examination; ORI = orientation; STM = short-term memory.

[a] 2-way analysis of covariance (ANCOVA) with age, sex and educational level as a covariates.

[38]. Nevertheless, variations in age, ethnicity, and methodology may also be involved.

There are some limitations to this study. Firstly, no data were available on the use of lipid-lowering medications. Previous studies have proposed that the effect of cholesterol level on cognition is bidirectional due to the influence of age [3]. The use of statins, a type of lipid-lowering drug, has also been reported to possibly reduce the risk of cognitive decline and developing AD [39], although the results are conflicting [40]. A long-term cohort study with treatment modification is needed to further clarify this effect. Secondly, regarding the decline in perception and psychomotor performance with increasing age, previous reports have shown an age-related effect on neuro-psychological tests [29]. Thus, the CASI and MMSE-CE scores have been analyzed with age as a covariate to reduce the influence of age in this study. Lastly, the relatively small sample size and cross-sectional design may have contributed to the marginal effect on cognition. Indeed, this phenomenon may be a diluted effect. As the participants are healthy according to clinical criteria, some with the risk genes will never develop dementia and some without the risk genes will eventually develop dementia. Furthermore, the CASI domain scores should be interpreted with more caution than the CASI total score because the domain scores are based on a smaller number of test items [25].

In conclusion, the present study reveals that ε4 carriers and individuals with the AA allele of CYP46 have decreased mental manipulation scores. There is also a combined effect of metabolic syndrome and ApoE ε4 alleles in subtle cognitive dysfunction among the Taiwanese Chinese population. Studies with long-term follow-up and serial assessments of metabolic syndrome may provide information to determine if both the metabolic syndrome and lipid-related genes increase the risk of cognitive decline.

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