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ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Dr. Antonio Corvino is a PhD in the Motor Science and Wellness Department at University of Naples "Parthenope". In 2008, he obtained his MD degree from the School of Medicine, Second University of Naples. Then, he completed a residency in Radiology in 2014 at University Federico II of Naples. In 2015, he undertook post-graduate training at Catholic University of Rome, obtaining the 2 nd level Master's degree in "Internal Ultrasound Diagnostic and Echo-Guided Therapies". In 2016-2018, he served on the directive board of Young Directive of Italian Society of Ultrasound in Medicine and Biology. His ongoing research interests involve ultrasound and ultrasound contrast media in abdominal and non-abdominal applications, *etc*. (L-Editor: Filipodia)

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ORIGINAL ARTICLE

Case Control Study

Metabolic syndrome, ApoE genotype, and cognitive dysfunction in an elderly population: A single-center, case-control study

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Abstract

BACKGROUND

Metabolic syndrome (MetS) is related to poor cognitive function. However, the results of previous studies were inconsistent, and whether the *ApoEε4* allele modifies the association remains unclear.

AIM

To elucidate the relationships among MetS, *ApoEε4*, and cognitive dysfunction in an elderly population in China.

METHODS

One hundred elderly patients with MetS and 102 age- and gender-matched controls were included in the study. Baseline clinical characteristics and biochemical index for glucose and lipid metabolism were obtained. The distribution of *ApoEε4* was assessed with PCR restriction fragment length polymorphism analysis. Cognitive function was evaluated by mini-mental status examination at the 1-year follow-up examination.

RESULTS

Compared with controls, MetS patients had worse cognitive function and decreased ability to participate in activities of daily life (P = 0.001 and 0.046, respectively). Patients with cognitive dysfunction had higher prevalence of MetS (62.1% *vs* 36.4%, P < 0.001) and were more likely to carry the *ApoEε4* allele (22.3% *vs* 10.1%, P = 0.019). Multivariate logistic regression analyses showed that diagnosis with MetS, severe insulin resistance, status as an *ApoEε4* carrier, higher systolic blood pressure, and larger waist circumference were risk factors for cognitive dysfunction (P < 0.05). Repeated-measures analysis of variance, performed with data collected at the 1-year follow-up, revealed continuous influences of MetS and *ApoEε4* on the deterioration of cognitive function (time × team, P < 0.001 for both).

comparable ethics standards.

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CONCLUSION

Diagnosis of MetS and *ApoEε4* carrier status were persistently associated with cognitive dysfunction among an elderly population in China.

Key Words: Metabolic syndrome; *ApoEε4*; Cognitive dysfunction; Elderly; Genotype; Case-control study

Core Tip: A case-control study was performed to evaluate the association between metabolic syndrome (MetS), *ApoEε4*, and cognitive dysfunction in an elderly population. With a multivariate analysis, we found that both MetS and status as an *ApoEε4* carrier were risk factors for cognitive dysfunction. Moreover, with repeated-measures analysis of variance performed with data collected at the 1-year follow-up, we found continuous influences of MetS and *ApoEε4* on the deterioration of cognitive function. These findings suggested that MetS and *ApoEε4* carrier status were persistently associated with cognitive dysfunction among an elderly population.

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INTRODUCTION

With accelerated aging observed in developed and developing countries, cognitive dysfunction has been established as an important contributor to morbidity and mortality worldwide[1,2]. Considerable proportions of elderly people display cognitive impairment, with a reported prevalence of > 20% in community-based elderly populations[3-6]. Prevalence varies depending on the characteristics of the studied population and the criteria for diagnosis. Patients with cognitive impairment are at higher risk for the development of Alzheimer's disease, which contributes to the loss of participation in activities of daily living (ADL), and are at an increased risk of accidents such as falls, ultimately leading to increased mortality. Current evidence suggests that the development of cognitive dysfunction is multifactorial, involving age, gender, personal education, economics, lifestyle, and comorbidities of somatic diseases, especially cerebrovascular disease[7-9]. Therefore, identification of modifiable risk factors for cognitive dysfunction is important for the early prevention of morbidity and mortality related to cognitive impairment, particularly in elderly populations.

Metabolic syndrome (MetS) is a cluster of metabolic disorders characterized by insulin resistance[10,11]. The components of MetS include obesity, hyperglycemia, dyslipidemia, and hypertension. The pathogenesis of the condition is related to an unhealthy lifestyle[12]. Patients with MetS are at an increased risk for many clinical disorders, including cardiovascular disease[13] and cancer[14]. The prevalence of MetS increases with age[15]. Most components of MetS have been associated with an increased risk for mild cognitive impairment and dementia[16,17], indicating that MetS may underlie cognitive dysfunction in the elderly. Although accumulating evidence suggests an association between MetS and cognitive decline in the elderly, the conclusions of previous studies were inconsistent. The factors that contribute to this heterogeneity of results remain to be identified[18].

The *ApoE* gene encodes apolipoprotein E, which is essential for the normal catabolism of triglyceride-rich lipoprotein constituents and mediates cholesterol metabolism in an isoform-dependent manner. Located on chromosome 19, the *ApoE* gene has three alleles: ε2, ε3, and ε4, with reported frequencies in the general population of 8%, 77%, and 15%, respectively. *ApoEε4* carrier status is associated with susceptibility to atherosclerosis[19] as well as increased risk for dementia and Alzheimer's disease[20]. We hypothesized that the distribution of *ApoEε4* expression

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could reveal an association between MetS and cognitive dysfunction in elderly people. Therefore, in this case-control study, we aimed to evaluate potential associations among MetS, *ApoEε4*, and cognitive dysfunction in an elderly population in China. We investigated potential interactions between MetS and *ApoEε4* as well as continuous influences of MetS and *ApoEε4* on the temporal deterioration of cognitive function.

MATERIALS AND METHODS

This study was designed as a single-center, case-control study. The protocol for the study was approved by the Ethics Committee of Xuanwu Hospital, Capital Medical University, No. [2108]112. All procedures performed in studies involving human participants were in accordance with the ethics standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethics standards. Written consent was obtained from all subjects included in the study.

Inclusion and exclusion criteria

Patients who were admitted to the Department of Geriatric Medicine at Xuanwu Hospital, Capital Medical University during the period from April 1, 2016 through August 31, 2018 were eligible for inclusion in the study. We aimed to evaluate cognitive function in elderly patients with *vs* without MetS and to investigate the potential role of *ApoE*. Ultimately, 100 MetS patients and 102 control subjects were included. Participants were included if they met all of the following criteria: (1) Elderly subjects with age ≥ 60 years at enrollment who were aware of the study purpose and procedure and agreed to participate; (2) Individuals without acute or severe clinical conditions; and (3) No diagnosis or previous history of stroke or transient ischemic attack. MetS was diagnosed in accordance with the criteria recommended by the Chinese Medical Association, which required positive findings in three of the following four domains[21]: (1) Overweight or obesity as indicated by body mass index of ≥ 25.0 Kg/m^2; (2) Hyperglycemia as indicated by fasting plasma glucose (FPG) ≥ 6.1 mmoL/L and/or postprandial plasma glucose ≥ 7.8 mmoL/L at 2 h on the oral glucose tolerant test, or confirmed diagnosis of diabetes mellitus; (3) Hypertension as indicated by systolic blood pressure (BP) ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg, or confirmed diagnosis of hypertension and previous treatment with antihypertensive medication; and (4) Dyslipidemia as indicated by plasma triglyceride (TG) ≥ 1.7 mmoL/L and/or reduced plasma high-density lipoprotein cholesterol (HDL-C) while fasting (< 0.9 mmoL/L in males and < 1.0 mmoL/L in females). Patients were excluded if they had the following conditions: (1) Aphasia, severe hearing loss, blindness, or severe discomfort, with inability to undergo a cognitive function evaluation; (2) Severe neurological diseases known to affect cognitive function, such as stroke, Parkinson disease, or brain tumor; (3) Severe mental disorder known to affect cognitive function or inability to undergo a cognitive evaluation (*e.g.*, severe depression, anxiety, psychiatry); (4) Long-term treatment with psychiatric medication; (5) Severe somatic disease (heart failure, renal dysfunction, or hepatic dysfunction), acute clinical status (acute myocardial infarction or infection), unstable clinical status (severe tachycardia or low BP), or malignant tumor with expected lifespan < 1 year; and (6) Refusal to undergo blood tests or cognitive evaluation.

Collection of baseline clinical data

After enrollment, baseline clinical data were collected for each included participant by a group of researchers who had been trained in standard procedures for data collection. Demographic variables, education status, professional information, socioeconomic status, and previous medical history were obtained *via* standard questionnaire, which was completed by participants with the assistance of researchers at the first face-to-face interview. Physical examinations were performed by trained physicians to obtain baseline measurements of height, weight, waist circumference, and systolic and diastolic BP. All measurements were obtained in a quiet room. After patients had fasted for at least 8 h, blood samples were obtained *via* cubital venous puncture for the measurement of biochemical parameters related to glucose and lipid metabolism. An automatic biochemical analyzer (Model 7600, Hitachi, Japan) was used to measure FPG, glycosylated hemoglobulin, alanine aminotransferase, plasma albumin, serum creatinine, uric acid, TG, total cholesterol, low-density lipoprotein cholesterol, HDL-C, and homocysteine. The fasting insulin was measured using a radioimmunoassay. All analyses were performed in the Department of Clinical

Laboratory at Xuanwu Hospital Capital Medical University. We calculated the homeostasis model of assessment for insulin resistance index (HOMA-IR) as an indicator of the severity of insulin resistance with the following equation: HOMA-IR = FPG (mmoL/L) × fasting insulin (mU/L)/22.5, as previously described[22]. Baseline clinical data collection and measurements of biochemical index were performed by researchers without knowledge of the MetS diagnosis.

Distribution of ApoE

Measurement of *ApoE* distribution was performed using a genomic DNA-based PCR-restriction fragment length polymorphism analysis. Briefly, genomic DNA was extracted from 5 mL venous blood samples in EDTA tubes, using a commercially available QIAGEN DNA extraction kit according to the manufacturer's instructions. Then, using a pair of PCR primers (upstream primer sequence: 5'-TAAGCTT GGCACGGCTGTCCAAGGA-3'; downstream primer sequence: 5'-ACAGAA TTCGCCCCGGCCTGGTACAC-3') synthesized by Sangon Biotech Company (Shanghai, China) and genomic DNA, PCR was performed in a reactive mixture of 20 μL with a commercially available PCR kit (Promega), according to the manufacturer's instructions. The amplification process consisted of initial denaturation at 95 °C for 3 min, followed by 35 cycles of denaturation at 95 °C for 1 min, subsequent cooling at 62 °C for 30 s, extension at 72 °C for 30 s, and final extension at 72 °C for 5 min. Negative controls without the addition of DNA were also included in every PCR run to assess potential contamination. A DNA fragment of 244 bp was obtained. Genotyping of the *ApoE* allele was performed by digesting the PCR product (15 μL) with 20 U of the Hha I (Thermo) restriction enzyme. The digested products were subjected to electrophoresis on 20% nondenatured polyacrylamide gel (70V for 6 h). The sizes of the fragments from polymorphic Hha I sites reflected the alleles of the *ApoE* genotype. Specifically, 91 bp and 81 bp indicated ε2/ε2; 91 bp and 48 bp indicated ε3/ε3; 72 bp and 48 bp indicated ε4/ε4; 91 bp, 81 bp, and 48 bp indicated ε2/ε3; 91 bp, 81 bp, 72 bp, and 48 bp indicated ε2/ε4; 91 bp, 72 bp, and 48 bp indicated ε3/ε4[23].

Cognitive function and ability to participate in ADL

Cognitive function was assessed by a trained physician at baseline and at the 1-year follow-up for each of the included subjects using a mini-mental status examination (MMSE) scale[24]. The MMSE scale allows researchers to evaluate six domains of cognitive function, including orientation, memory, attention, and calculation. Maximum score on the MMSE scale was 30; cognitive dysfunction was considered in the context of education. Specifically, an MMSE score < 17 indicates cognitive dysfunction for subjects with education of < 1 yr; an MMSE score < 20 indicates cognitive dysfunction for those with education of 1-6 years; and an MMSE score < 24 indicates cognitive dysfunction for those with education ≥ 7 yrs. Mild cognitive dysfunction was considered for those with MMSE scores of 24-27 points. We used the Barthel index to assess the ability to participate in ADL among the elderly patients included in the study. The Barthel index includes assessment of six basic living activities: Dressing, mobilizing, washing, bathing, toileting, and eating[25]. Higher scores on the Barthel index (maximum = 100 points) indicated improved ability to participate in ADL.

Statistical analyses

Continuous variables were tested for normality. Normally distributed data were compared using the t-test and presented as means ± standard deviation. Non-normally distributed data were compared with nonparametric tests and presented as median values with interquartile ranges. Categorized variables were presented as numbers and proportions. Between-group comparisons were performed with the chi-square test. Multivariable logistic regression was performed to identify the predictors of cognitive dysfunction among elderly participants. A factorial test was used to evaluate the potential interaction of MetS and *ApoEε4* in predicting cognitive dysfunction among this patient population. Finally, repeated-measures analysis of variance was applied to evaluate the potential correlations between MetS and *ApoEε4* in predicting changes in cognitive function at the 1-year follow-up. A $P < 0.05$ was statistically significant. We used SPSS 17.0 software for all analyses.

RESULTS

Baseline characteristics in elderly patients with vs without MetS

The baseline characteristics of included subjects with or without MetS were shown in Table 1. Briefly, elderly patients with or without MetS were matched for baseline characteristics such as age, gender, education status, professional characteristics, living status, and smoking and alcohol habits (all $P > 0.05$). Elderly patients with MetS were likely to have impaired glucose and lipid metabolism, including higher FPG, fasting insulin, HOMA-IR, glycosylated hemoglobulin, TG, and total cholesterol, and lower HDL-C (all $P < 0.05$), which was consistent with a diagnosis of MetS. Elderly patients with MetS also showed a trend toward higher body mass index and low-density lipoprotein cholesterol ($P = 0.060$ and $P = 0.058$, respectively). Cognitive function and ability to participate in ADL were decreased in elderly patients with MetS, as reflected by significant decreases in MMSE scores and ability to participate in ADL among these patients ($P = 0.001$ and $P = 0.046$, respectively). The use of recommended MMSE cutoff values to diagnose cognitive dysfunction showed that cognitive dysfunction was more common among elderly patients with MetS compared with controls (64.0% *vs* 38.2%, $P < 0.001$). *ApoEε4* carrier status tended to be more common among elderly patients with MetS compared with elderly participants without MetS (21.0% *vs* 11.8%, $P = 0.076$).

Prevalence of MetS and ApoEε4 in patients with vs without cognitive dysfunction

The prevalence of MetS and *ApoEε4* in patients with *vs* without cognitive dysfunction were shown in Table 2. MetS and *ApoEε4* were more common among the 99 patients diagnosed with cognitive dysfunction at baseline (62.1% *vs* 36.4%, $P < 0.001$; 22.3% *vs* 10.1%, $P = 0.019$, respectively) compared to those without cognitive dysfunction.

Predictors of cognitive dysfunction in elderly patients

Multivariable logistic regression analyses were performed to identify independent predictors of cognitive dysfunction in elderly patients (Table 3). In our elderly patient cohort, diagnosis with MetS, higher HOMA-IR, *ApoEε4* carrier status, higher systolic BP, and larger waist circumference were found to be risk factors for cognitive dysfunction (all $P < 0.05$). The results of factorial analyses showed that MetS and *ApoEε4* carrier status showed no potential interaction in predictions of cognitive dysfunction at baseline ($F = 2.388$, $P = 0.124$).

Correlations between MetS and ApoEε4 in predicting cognitive dysfunction

We performed repeated-measures analysis of variance to elucidate potential correlations between MetS and *ApoEε4* in predicting cognitive dysfunction during the 1-year follow-up (Table 4). Continuous effects of MetS and *ApoEε4* carrier status on the deterioration of cognitive function at the 1-year follow-up were recorded (time × team, both $P < 0.001$).

DISCUSSION

In this study, we found that diagnosis with MetS and *ApoEε4* carrier status were potential risk factors related to cognitive dysfunction in an elderly population in China. No significant interaction between these factors was observed in relation to cognitive dysfunction in our cohort. The effects of MetS and *ApoEε4* on the deterioration of cognitive function over a 1-year follow-up period were continuous in this study population ($P < 0.05$). Taken together, the results presented above show that, in our cohort of elderly Chinese patients, diagnosis with MetS and *ApoEε4* carrier status were independently associated with cognitive dysfunction. The effect persisted over the course of 1-year ($P < 0.05$).

Although great efforts have been made over recent decades to elucidate the potential association between MetS and cognitive impairment among elderly individuals, the findings reported have been inconsistent. In a recently published systematic review, the authors cited 25 observational studies that reported an association between MetS and cognitive impairment in the elderly. The authors reported substantial heterogeneity among studies, including differences in the diagnostic criteria for MetS, the methodology used for cognitive measurements, the duration of follow-up, and adjustments for potential confounding factors. These causes of heterogeneity prevented the authors from performing a quantitative meta-analysis[18]. The authors concluded that evidence for an effect of MetS on cognitive

Table 1 Baseline study characteristics in elderly patients with *vs* without metabolic syndrome

	Control, *n* = 102	MS, *n* = 100	t/χ^2	*P* value
Mean age (years)	75.32 ± 7.55	76.45 ± 6.90	0.443	0.506
Male, *n* (%)	66 (64.7)	67 (67.0)	0.118	0.731
Educated, *n* (%)	95 (93.1)	89 (89.0)	1.065	0.302
Intelligent working, *n* (%)	90 (88.2)	80 (80.0)	2.569	0.109
Living alone, *n* (%)	10 (9.8)	14 (14.0)	0.849	0.357
Current smoking, *n* (%)	40 (39.2)	47 (47.0)	1.248	0.264
Alcohol drinking, *n* (%)	14 (13.7)	18 (18.0)	0.692	0.405
Systolic BP (mmHg)	121.00 ± 11.29	150.30 ± 14.50	8.032	0.005
Diastolic BP (mmHg)	71.68 ± 6.82	78.57 ± 8.42	5.304	0.022
Waist circumference (cm)	82.64 ± 6.87	93.44 ± 8.48	5.529	0.020
BMI (kg/m^2)	22.88 ± 2.76	26.39 ± 2.37	3.583	0.060
FPG (mmoL/L)	6.09 ± 1.54	7.73 ± 2.03	5.581	0.019
FINS (mIU/L)	10.46 ± 5.34	14.46 ± 6.67	5.188	0.024
HOMA-IR	2.96 ± 2.02	5.17 ± 3.40	17.449	< 0.001
HbA1c (%)	3.71 ± 1.53	4.67 ± 1.91	5.749	0.017
ALT (IU/L)	19.98 ± 10.20	22.04 ± 11.51	1.119	0.292
ALB (g/L)	37.97 ± 4.98	38.49 ± 4.28	0.721	0.580
SCr (μmoL/L)	80.72 ± 20.31	79.94 ± 21.86	1.316	0.253
UA (μmoL/L)	327.64 ± 92.27	325.86 ± 90.06	0.014	0.907
TG (mmoL/L)	1.50 ± 0.74	2.20 ± 1.10	4.069	0.045
TC (mmoL/L)	3.86 ± 0.84	4.14 ± 1.14	4.471	0.031
LDL-C (mmoL/L)	2.10 ± 0.70	2.60 ± 0.84	3.632	0.058
HDL-C (mmoL/L)	1.55 ± 0.52	1.28 ± 0.38	-1.706	0.003
HCY (μmoL/L)	13.41 ± 4.90	13.95 ± 4.54	1.743	0.188
MMSE scale	25.93 ± 3.26	21.50 ± 4.51	11.268	0.001
ADL score	90.25 ± 14.20	82.30 ± 16.06	4.038	0.046
Cognitive dysfunction, *n* (%)	39 (38.2)	64 (64.0)	13.413	< 0.001
ApoEε4 allele, *n* (%)	12 (11.8)	21 (21.0)	3.151	0.076

Continuous data are presented as means and standard deviations. Categorized data are presented as numbers and percentiles. MS: Metabolic syndrome; BP: Blood pressure; BMI: Body mass index; FPG: Fasting plasma glucose; FINS: Fasting insulin; HOMA-IR: Homeostasis model of assessment for insulin resistance index; HbA_{1c}: Glycosylated hemoglobulin; ALT: Alanine aminotransferase; ALB: Albumin; SCr: Serum creatinine; UA: Uric acid; TG: Triglyceride; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; HCY: Homocysteine; MMSE: Mini-mental status examination; ADL: Activities of daily living.

decline among elderly individuals was vastly inconsistent and highlighted the importance of identifying factors that may affect the association between MetS and cognitive dysfunction in the elderly[18].

Based on published evidence that *ApoEε4* carrier status affects risk for cognitive decline and/or dementia in the elderly, we aimed to evaluate whether *ApoEε4* carrier status may modify the association between MetS and cognitive dysfunction in elderly Chinese individuals[26]. This study, which used validated criteria for the diagnosis of MetS and evaluation of cognitive function, showed that MetS and *ApoEε4* are independent risk factors for cognitive dysfunction in elderly Chinese individuals. This is consistent with previous findings from observational studies that evaluated the association between MetS and cognitive function, after fully adjusting for *ApoEε4* carrier status. In an early prospective cohort study of 1352 community-living older Chinese adults without cognitive impairment or cardiovascular disease at baseline,

Table 2 Prevalence of metabolic syndrome and *ApoEε4* in patients with *vs* without cognitive dysfunction

	Normal cognitive function, *n* = 99	Cognitive dysfunction, *n* = 103	χ^2 value	*P* value
MetS, *n* (%)	36 (36.4)	64 (62.1)	13.413	< 0.001
ApoEε4, *n* (%)	10 (10.1)	23 (22.3)	5.523	0.019

MetS: Metabolic syndrome.

Table 3 The association between clinical variables and cognitive dysfunction from the results of logistic regression analyses

Variables	β	SE	Wald	*P* value	OR
MetS	1.573	0.894	4.215	0.038	2.771
HOMA-IR	1.144	0.510	5.037	0.025	3.140
ApoE ε4	1.765	0.798	4.896	0.027	5.844
Systolic BP (mmHg)	0.068	0.030	4.935	0.026	1.070
Waist circumference (cm)	0.270	0.072	13.864	< 0.001	1.131

MetS: Metabolic syndrome; HOMA-IR: Homeostasis model of assessment for insulin resistance index; BP: Blood pressure.

Table 4 Potential correlations between metabolic syndrome and *ApoEε4* and temporal changes in cognitive dysfunction during 1-year follow-up: Results of the repeated-measure analysis of variance

Team	*n*	F/*P* values (time)	F/*P* values (time × team)	F/*P* values (team)
MetS				
Yes; No	100, 102	324.15/< 0.001	96.57/< 0.001	86.43/< 0.001
ApoE ε4				
Yes; No	33, 169	351.94/< 0.001	77.90/< 0.001	24.65/< 0.001

MetS: Metabolic syndrome.

which controlled for potential confounding factors (age, gender, education, smoking, alcohol use, depressive symptoms, *ApoEε4* status, level of recreational activity, baseline MMSE score, and length of follow-up), MetS at baseline was found to be an independent risk factor for the development of cognitive decline[27].

Another cohort study, conducted in Singapore, used multivariate regression analysis to show that MetS was associated with increased risk for cognitive impairment (OR = 1.77), after adjustment for potential confounding factors (*e.g.*, *ApoEε4* status). The authors found that the association between MetS and cognitive impairment was particularly strong in elderly individuals who carried *ApoEε4* (OR = 3.35) but remained significant in elderly participants who did not carry *ApoEε4*[28]. This finding suggested a potential synergistic effect between MetS and *ApoEε4* in predicting cognitive decline among the study population. Similarly, significant interactive action between MetS and *ApoEε4* in predicting cognitive dysfunction was confirmed in a previous study in Taiwan, China[29]. This study included 209 mentally healthy middle-aged and older adults and showed that MetS may play a role in subtle cognitive dysfunction in *ApoEε4* carriers among Taiwanese Chinese. Taken together, these results strongly suggested that MetS and *ApoEε4* may have an interaction in the pathogenesis of cognitive dysfunction.

The results of our study differ from the findings above. Although MetS and *ApoEε4* carrier status were shown to be independent risk factors for cognitive dysfunction in elderly Chinese individuals, no significant interaction between these factors was observed. The inconsistency between our findings and those reported previously regarding a synergistic effect of MetS and *ApoEε4* may be explained by differences in study design and patient characteristics. For example, our conclusion regarding the interaction between MetS and *ApoEε4* in predicting cognitive dysfunction is based on

cross-sectional analysis, which is different from the cohort design of previous studies. Moreover, we excluded patients with previous stroke or transient ischemic attack from our study. Such patients were not excluded from previous studies[30] and are more likely to experience cognitive effects related to *ApoEε4* expression.

Metabolic disorders are important pathophysiological basis of diseases related to cognitive impairment, such as Alzheimer's disease[31,32]. Vascular dysfunction and metabolic disorders are two fundamental pathophysiological mechanisms of Alzheimer's disease[33]. Insulin resistance-related inflammation and oxidative stress-related injury may directly lead to the impairment of cognitive function[31,34]. Moreover, secondary damage caused by vascular disease may further impair cognitive function[31]. Similar pathological changes, such as the accumulation of β-amyloid protein and phosphorylation of Tau protein, two fundamental changes in the neurons of patients with Alzheimer's disease, have been observed in the pancreatic islets of diabetic patients ("type 3 diabetes")[35]. The exact molecular pathways underlying the association between metabolic disorders and cognitive dysfunction remain to be uncovered. Further research is needed to develop novel strategies to prevent cognitive decline in the elderly.

Another interesting finding of our study is the continuous effect of MetS on the deterioration of cognitive function over a 1-year follow-up period. These findings highlight the importance of therapeutics to improve MetS-related metabolic effects on cognitive function. This result was confirmed in a recent case study of a 38-year-old male with MetS and *ApoEε4* carrier status, who had a family history of Alzheimer's disease and early memory impairment[36]. After initiation of a ketogenic diet and high-intensity interval training for 10 wk, the patient's score on the Montreal Cognitive Assessment improved significantly. The patient's levels of a variety of MetS-related markers (*e.g.*, HOMA-IR, TG/HDL-C) decreased as well[36]. Moreover, a preliminary study showed that combined antihypertensive treatment positively affected 24 h BP profile, increased cerebral blood flow, and improved cognitive function in patients with MetS[37]. These findings suggest that treatment for MetS may improve cognitive status in these patients. Additional clinical trials in this field are warranted.

Limitations and clinical perspectives for future studies

Our study has limitations, which should be considered when interpreting the results. First, as a small-scale, single-center, case-control study, our study may lack the statistical power to detect correlations between risk factors for cognitive dysfunction, such as smoking[38] and alcohol use[39]. Our results should be validated in large-scale multicenter studies. Second, although we applied a multivariate model for the logistic regression analysis, this observational study may have included residual confounding factors for the association between MetS and *ApoEε4* and the prevalence of cognitive dysfunction. Therapeutics against insulin resistance and dyslipidemia (*e.g.*, statins) may be associated with cognitive decline[40]. Therefore, statin therapy may be important to modify the association between MetS or *ApoEε4* and cognitive dysfunction. Future studies are warranted to investigate whether the association between MetS, *ApoEε4*, and cognitive dysfunction remains after analysis that incorporates therapeutic strategies such as statins. Third, a causative relationship among MetS, *ApoEε4*, and cognitive dysfunction could not be derived, because the study had an observational design. Although we found that the effects of MetS on cognitive dysfunction continued over 1 year of follow-up, future studies will be necessary to determine whether these influences persisted over the long term. Furthermore, high-quality clinical trials are needed to determine whether optimizing the metabolic factors involved in MetS could favorably affect cognitive status in these patients[41]. From a clinical perspective, the results of such an investigation would have great significance. Finally, additional efforts are needed to determine how best to prevent cognitive decline in people carrying *ApoEε4*[26].

CONCLUSION

In conclusion, the results of our study showed that diagnosis with MetS and *ApoEε4* carrier status were independently associated with cognitive dysfunction in the included elderly Chinese population. This effect persisted throughout 1 year of follow-up. Additional studies are needed to evaluate the potential benefits of therapeutic strategies that target MetS in relation to the development of cognitive dysfunction in elderly individuals as well as the potential modifying influence of *ApoEε4* carrier status.

ARTICLE HIGHLIGHTS

Research background

Cognitive impairment is a serious public problem in the elderly population. Metabolic syndrome (MetS) is increasingly prevalent in the global population. It remains unknown whether MetS is associated with cognitive decline in elderly, and whether distribution of the *ApoEε4* allele may modify the association.

Research motivation

To provide pilot evidence regarding the roles of MetS and distribution of *ApoEε4* allele with the occurrence of cognitive impairment in elderly population, and to improve the understanding of the association between metabolic components, genetic factors, and cognitive decline.

Research objectives

To clarify the association between MetS, distribution of *ApoEε4* allele, and cognitive impairment in an elderly Chinese population and the continuous influence of MetS and distribution of *ApoEε4* allele on cognitive function within 1 year.

Research methods

An age- and gender-matched case-control study was performed. The distribution of *ApoEε4* was assessed with PCR fragment length polymorphism analysis. Cognitive function was evaluated by mini-mental status examination at the 1-year follow-up examination.

Research results

MetS and *ApoEε4* carrier status were potential risk factors related to cognitive dysfunction in an elderly population. No significant interaction between MetS and *ApoEε4* was observed. The effects of MetS and *ApoEε4* on the deterioration of cognitive function over a 1-year follow-up period were continuous.

Research conclusions

MetS and *ApoEε4* carrier status were independently associated with cognitive dysfunction at baseline and within 1 year in an elderly population.

Research perspectives

People with MetS and *ApoEε4* carrier status may have a higher risk of cognitive decline. These results may be helpful for the identification of elderly people at high risk for cognitive decline, and targeted intervention against these factors may be beneficial for cognitive function in these people.

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