

Associations of vascular risk factors, APOE ϵ 4 allele, and TOMM40 G allele with cognitive function in Chinese older adults: a community-based study

Wenjun Gui

Chinese Academy of Sciences

Chengxuan Qiu

Karolinska Institutet-Stockholm University

Juan Li (✉ lijuan@psych.ac.cn)

Chinese Academy of Sciences

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Abstract

Background : The associations of vascular risk factors (VRFs) , apolipoprotein E (APOE) ϵ 4 allele, and translocase of outer mitochondrial membrane 40 (TOMM40) G allele with cognitive function have been investigated mostly in western societies. In the present study, we sought to examine the associations of VRFs, APOE ϵ 4 allele, and TOMM40 G allele (rs2075650) with global cognitive function among Chinese older adults, with a focus on potential interactions between VRFs and the susceptibility genes.

Methods : This is a cross-sectional study that included 422 participants (mean age 69.2 years, 54.3% female) in the China Longitudinal Ageing Study , who were free of dementia. Data were collected through interviews, clinical examinations, and laboratory tests. The clustering of multiple VRFs was scored by counting the number of VRFs potentially related to cognitive function. Global cognitive function was assessed with the Mini-Mental State Examination (MMSE). Data were analyzed with multiple general linear regression models.

Results : Physical inactivity and diabetes were independently associated with performance lower MMSE score ($p < 0.05$). Moreover, physical inactivity interacted with APOE ϵ 4 and TOMM40 G allele (rs2075650), and diabetes interacted with TOMM40 G allele to affect cognitive function, such that having physical inactivity in combination with either APOE ϵ 4 allele or TOMM40 G allele, or having diabetes and TOMM40 G allele, compared to having neither, was significantly associated with markedly lower MMSE scores ($p < 0.05$). Finally, when four modifiable VRFs (i.e., current smoking, physical inactivity, high LDL-C, and diabetes) were aggregated, an increasing number of having these factors was associated with a decreasing MMSE score in a dose-response manner (p for trend < 0.05).

Conclusion : Some VRFs (e.g., physical inactivity and diabetes), when concurrently occurring with APOE ϵ 4 or TOMM40 G allele, are associated with substantially poor performance in global cognitive function among the Chinese elderly .

Background

The proportion of older people has been growing rapidly in China over the past half-century, alongside social and economic development. In 2010, there were 178 million people aged 60 years and older in China, accounting for approximately 13.3% of the total population. Therefore, the age-related disorders such as Alzheimer's disease (AD) and dementia have posed a tremendous burden to individuals and the society at large in China [1, 2]. Recently, great efforts have been made to identify modifiable risk factors for early-stage cognitive disorders, such as cognitive impairment and cognitive decline, which may help identify at-risk individuals and further facilitate the development of interventions to delay the onset of dementia. The associations of individual vascular risk factors (VRFs) and clustering of multiple VRFs with poor cognitive function have been well established in western countries [3, 4]. In China, some studies have reported the associations of individual VRFs (e.g., hypertension and diabetes) with cognitive impairment [5, 6]. However, very few studies have examined the association of clustering of multiple

VRFs with global cognitive impairment. Modifiable or manageable VRFs often coexist among the elderly, and an aggregation of multiple VRFs plays a critical role in cognitive impairment and cognitive decline [7]. Thus, exploring the association between clustering of multiple VRFs and cognitive function among Chinese older adults is of high relevance for developing the appropriate strategies for the prevention of cognitive impairment and dementia in China.

The $\epsilon 4$ allele of the apolipoprotein E (APOE) gene is a known genetic risk factor for AD and global cognitive decline in old age. Evidence from meta-analysis has suggested that the APOE $\epsilon 4$ allele was associated with poorer performance on tests of global cognitive function [8, 9]. However, most of the studies have been carried out among western societies, and very few studies are carried out in Chinese elderly people. In addition, translocase of outer mitochondrial membrane 40 (TOMM40) is approximately 15 kb upstream to APOE and plays an essential role in mitochondrial survival. Several single-nucleotide polymorphisms (SNPs), such as rs2075650, are found to be associated with the risk of AD. Recently, TOMM40 rs2075650 G (TOMM40 G) has been identified as a high-risk allele associated with the risk of developing AD in different populations, including Han Chinese [10, 11]. However, few studies have explored the contribution of TOMM40 G to cognitive dysfunction and the results are inconsistent when different populations are examined. For example, the genome-wide association study has revealed that TOMM40 G is associated with cognitive aging in the Swedish cohorts, but not in the UK cohorts [12]. To date, the role of TOMM40 G in cognitive function among Chinese older adults is still unclear.

In addition, emerging evidence has indicated that VRFs and susceptibility genes could interact synergistically to exacerbate cognitive decline. For instance, some studies have reported that APOE $\epsilon 4$ allele may interact with VRFs (e.g., hypertension and diabetes) to adversely affect global cognitive function [13–15] and specific cognitive domains such as memory and executive function [16, 17]. In addition, no study has examined the interaction of TOMM40 G allele with VRFs on global cognitive function. Of note, population-based studies that explore potential interactions of VRFs with susceptibility genes on cognition among Chinese population are generally lacking.

Therefore, in the present study, we aim (1) to examine associations of individual VRFs and clustering of multiple VRFs, APOE $\epsilon 4$ allele, and TOMM40 G allele with global cognitive function among community-dwelling Chinese elderly and (2) to explore the interactions between VRFs and the two susceptibility genes on global cognitive function. We hypothesize that clustering of multiple VRFs, APOE $\epsilon 4$ allele, and TOMM40 G allele is associated with poor global cognitive performance and that carrying susceptibility genes may strengthen the associations of VRFs with poor cognitive function.

Methods

Study participants

The study participants were from the China Longitudinal Ageing Study, and details of the study design and data collection procedures have been fully described previously [18]. Briefly, at baseline (2011), 473

permanent residents (age ≥ 60 years) were randomly selected from XiCheng and ChaoYang Districts in Beijing, which represented the old downtown and the newly developed area, respectively. Of these, 40 participants were excluded due to lack of blood samples and additional 11 participants were excluded owing to probable AD or other dementia defined according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria (DSM-IV) [19], leaving 422 participants for the final analysis of cross-sectional associations.

This study was approved by the Ethics Committee at the Institute of Psychology, Chinese Academy of Sciences, Beijing, China. Written informed consent was given by each participant at each visit.

Data collection

At baseline, research assistants with psychological background collected data on demographics, cardiovascular or lifestyle-related factors (e.g., smoking, alcohol consumption, and leisure activity). Physical exercise was measured via the question "How often do you regularly participate in physical exercise at least 20 minutes (never, 1–3 days/week, 4–6 days/week, every day)?" Psychiatrists conducted the clinical assessment, including health history and use of medications, a routine physical examination, as well as neuropsychological tests (e.g., Neuropsychiatric Inventory and the Clinical Dementia Rating). Depressive symptoms were assessed using the 30-item Geriatric Depression Scale (GDS-30) [20]. Weight and height were measured in light clothes with no shoes. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Arterial blood pressure was measured twice on the right arm in a sitting position, and the mean of both measurements was used for the analysis.

After overnight fasting, peripheral blood samples were taken. Plasma glucose, total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were measured using standard enzymatic methods on routine automated chemistry systems. Genomic DNA was isolated from whole blood samples.

Definitions of vascular factors

Smoking and alcohol intake were dichotomized into current and non-current (never and former). Physical inactivity was defined as participating in any exercise < 3 times/week during leisure time. Obesity was defined as a BMI ≥ 28 kg/m², a commonly recommended cut-off point for Chinese adults [21]. High TC was defined as TC > 6.2 mmol/l or use of hypolipidemic drugs, high TG as TG ≥ 2.3 mmol/l or receiving hypolipidemic drugs, low HDL-C as HDL-C < 1.0 mmol/l in men, or HDL-C < 1.3 mmol/l in women or use of hypolipidemic drugs, and high LDL-C as LDL-C ≥ 4.1 mmol/l or using hypolipidemic drugs [22]. Diabetes was defined as fasting plasma glucose ≥ 7.0 mmol/l or the current use of oral blood glucose-lowering medications or insulin injections [23]. Hypertension was defined as having a self-reported history of hypertension, current use of antihypertensive medication, or blood pressure $\geq 140/90$ mm Hg [24].

Genotyping

APOE and TOMM40 were genotyped using the Sequenom iPLEX gold assay and the MassARRAY MALDI-TOF mass spectrometry platform (San Diego, CA, USA). APOE genotype was dichotomized as carriers vs.

non-carriers of the APOE ϵ 4 allele, and TOMM40 G status as carriers vs. non-carriers of the rs2075650 G allele.

Definitions of Covariates.

The presence of depressive symptoms was defined as the GDS-30 score > 10. Heart disease was defined as having myocardial infarction, atrial fibrillation, heart failure, or angina.

Assessment of global cognitive function

Global cognitive functioning was assessed with the Chinese version of the Mini-Mental State Examination (MMSE). Most items of it were translated literally from the original version without modification, while some items were adapted to meet the Chinese cultural context [25]. It is a validated and widely used test of assessing global cognitive functioning with orientation, memory, attention-calculation, language, and registration components. The total MMSE score ranges from 0 to 30, with higher scores denoting better cognitive performance.

Statistical analysis

The participants' characteristics by APOE ϵ 4 and TOMM40 G status were compared using independent t -tests for continuous variables and χ^2 tests for categorical variables.

Multivariable linear regression models were used to analyze the associations of MMSE score with various factors. Firstly, we estimated the β coefficients and 95% confidence interval (CI) of MMSE score associated individual and clustering of multiple VRFs, APOE ϵ 4 allele, and TOMM40 G allele. Clustering VRFs was scored by summing up the total number of VRFs that were potentially associated with a lower MMSE score in multivariable linear regression analysis [26]. In order not to miss any potential risk factors associated with MMSE score, we used a conservative p value of 0.35 for inclusion of variables, as previously reported [27, 28]. The clustering of multiple VRFs score was treated as continuous and categorical variables in the analysis.

We also assessed the interactions of VRFs with susceptibility genes on cognitive performance by simultaneously including the two independent variables and their cross-product terms in the same model. To examine the joint effects of VRFs with susceptibility genes, we divided subjects into 4 groups: those with no VRFs or susceptibility genes (reference), with only VRFs (e.g., diabetes), only susceptibility genes (e.g., APOE 4 allele), or both.

We reported results from two models: model 1 was adjusted for demographic variables (i.e., age, sex, and education) and model 2 was further adjusted for the presence of depressive symptoms and heart disease. IBM SPSS Statistics 21.0 (IBM Corp Armonk, NY) for Windows was used for all statistical analyses.

Results

Characteristics of the study participants

Of the 422 participants, the mean age was 69.2 (SD, 6.2) years, and 54.3% were women. The APOE ϵ 4 allele carriers and non-carriers did not differ significantly in the mean age and years of education, or in the distribution of sex, current smoking, alcohol intake, physical inactivity, obesity, high cholesterol, high triglycerides, low HDL-C, high LDL-C, hypertension, diabetes, depression and heart disease (for all comparisons, $p > 0.05$) (Table 1). Furthermore, there were no significant differences between TOMM40 G allele carriers and non-carriers on the above factors (for all comparisons, $p > 0.05$), except for high LDL-C ($p = 0.05$) (Table 1).

Table 1
 Characteristics of the study participants at baseline (n = 422)

Baseline characteristics	Total Sample	APOE ε4 allele		p value	TOMM40 G allele		p value
		No	Yes		No	Yes	
No. of subjects	422	359	63		341	81	
Age, y, mean (SD)	69.0(6.2)	69.8(6.2)	70.14(6.5)	0.68	69.8(6.3)	70.1(6.3)	0.76
Women, n (%)	229(54.3)	194(55.0)	35(50.7)	0.52	184(54.0)	45(55.6)	0.80
Education, y, mean (SD)	12.5(4.8)	12.5(4.8)	12.7(4.5)	0.78	12.6(4.7)	12.3(4.9)	0.64
Current smoking, n (%)	52(12.3)	45(12.7)	7(10.1)	0.55	46(13.5)	6(7.4)	0.13
Current drinking, n (%)	50(11.8)	42(11.9)	8(11.6)	0.94	39(11.4)	11(13.6)	0.59
Physical inactivity, n (%)	97(23.0)	78(22.1)	19(27.5)	0.33	77(22.6)	20(24.7)	0.69
Obesity, n (%)	66(15.6)	56(15.9)	10(14.5)	0.77	51(15.0)	15(18.5)	0.43
High cholesterol, n (%)	95(22.5)	76(21.5)	19(27.5)	0.30	71(20.8)	24(29.6)	0.09
High triglycerides, n (%)	110(26.1)	88(24.9)	22(31.9)	0.23	83(24.3)	27(33.3)	0.10
Low HDL-C, n (%)	160(37.9)	134(38.0)	26(37.7)	0.97	104(37.8)	43(35.8)	0.76
High LDL-C, n (%)	96(22.7)	76(21.5)	20(29.0)	0.18	71(20.8)	25(30.9)	0.05
Hypertension, n (%)	254(60.2)	214(60.6)	40(58.0)	0.68	204(59.8)	50(61.7)	0.75
Diabetes, n (%)	82(19.4)	65(18.4)	17(24.6)	0.23	64(18.8)	18(22.2)	0.48
Depressive symptoms, n (%)	59(14.0)	46(13.0)	13(18.8)	0.20	45(13.2)	14(17.3)	0.34
Heart disease n (%)	69(16.4)	58(16.4)	11(15.9)	0.92	56(16.4)	13(16.0)	0.94

Abbreviations: APOE = apolipoprotein E; TOMM40 = translocase of outer mitochondrial membrane 40; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol

(Insert Table 1 here)

Associations of individual VRFs and VRF burden with MMSE score

Of individual VRFs, physical inactivity and diabetes were significantly associated with a low MMSE score (all $p < 0.05$). Current smoking and high LDL-C were potentially associated with a low MMSE score when a conservative p -value of 0.35 was considered (Table 2, models 1 and 2). None of alcohol intake, obesity, high cholesterol, high triglycerides, low HDL-C, hypertension, and APOE $\epsilon 4$ allele was associated with the MMSE score at the level of $p < 0.35$ (Table 2, models 1 and 2).

Table 2

Associations of MMSE score with vascular risk factors, APOE $\epsilon 4$ allele, and TOMM40 G allele (n = 422)

Vascular risk factors and susceptibility genes	β coefficient (95% confidence interval), MMSE score			
	Model 1 ^a	p	Model 2 ^a	p
Current smoking	-0.50(-1.32, 0.33)	0.24	-0.52(-1.33,0.31)	0.22
Alcohol intake	0.19(-0.64, 1.01)	0.66	0.21(-0.61, 1.02)	0.62
Obesity	-0.12(-0.82, 0.58)	0.74	-0.14(-0.84, 0.55)	0.69
Physical inactivity	-0.77(-1.36, -0.17)	0.01	-0.70(-1.30, -0.11)	0.02
High total cholesterol	-0.15(-0.76, 0.47)	0.65	-0.21(-0.83, 0.41)	0.51
High triglycerides	-0.11(-0.69, 0.47)	0.71	-0.16(-0.74, 0.42)	0.59
Low HDL-C	-0.05(-0.58,0.48)	0.86	-0.11(-0.64,0.42)	0.69
High LDL-C	-0.24(-0.86, 0.37)	0.43	-0.31(-0.92, 0.31)	0.33
Hypertension	0.41(-0.10, 0.93)	0.12	0.36(-0.16, 0.88)	0.18
Diabetes	-1.18(-1.81, -0.55)	0.001	-1.14(-1.78, -0.51)	0.001
APOE $\epsilon 4$ allele	-0.23(-0.93, 0.47)	0.52	-0.24(-0.94, 0.47)	0.51
TOMM40 G allele	-0.59(-1.22, 0.05)	0.07	-0.56(-1.19, 0.07)	0.08
Abbreviations: APOE = apolipoprotein E; TOMM40 = translocase of outer mitochondrial membrane 40; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol				
^a Model 1 was controlled for age, sex, and education, and model 2 was additionally controlled for presence of depressive symptoms and heart disease.				

When the four VRFs (i.e., current smoking, physical inactivity, high LDL-C, and diabetes) were counted to calculate the VRF score, as a continuous variable (0–4), an increasing VRF score was significantly associated with a lower MMSE score ($p < 0.001$) (Table 3). As a categorical variable (categorized into 0, 1, and ≥ 2), having 2 or more of these VRFs, in comparison with having none, was significantly associated with lower MMSE score, even when further adjusting for the presence of depressive symptoms and heart disease (p for trend < 0.001) (Table 3, models 1 and 2).

Table 3
Associations of MMSE score with clustering multiple vascular risk factors (n = 422)

No. of vascular risk factors ^a	β coefficient (95% confidence interval), MMSE score			
	Model 1 ^b	<i>p</i>	Model 2 ^b	<i>p</i>
As a continuous variable (0–4)	-0.59 (-0.89, -0.29)	0.001	-0.60 (-0.90, -0.30)	0.001
As a categorical variable				
0 (n = 185)	0.00 (Reference)		0.00 (Reference)	
1 (n = 162)	-0.11 (-0.65, 0.43)	0.70	-0.12 (-0.67, 0.42)	0.66
≥ 2 (n = 75)	-1.45 (-2.15, -0.76)	0.001	-1.49 (-2.19, -0.79)	0.001
<i>P</i> for linear trend	< 0.001		< 0.001	
^a Vascular risk factors included current smoking, physical inactivity, high LDL-C, and diabetes.				
^b Model 1 was controlled for age, sex, education, and model 2 was additionally controlled for the presence of depressive symptoms and heart disease.				

Associations of susceptibility genes with MMSE score

TOMM40 G allele was marginally associated with a low MMSE score ($\beta=-0.59$, $p = 0.07$), whereas APOE $\epsilon 4$ allele was not associated with a low MMSE score ($\beta=-0.23$, $p = 0.52$) when age, sex, and education were adjusted for (Table 2, model 1). The results were virtually unchanged when further adjusting for the presence of depressive symptoms and heart disease (Table 2, model 2).

Interactions between susceptibility genes and vascular risk factors

There was a statistical interaction of the APOE $\epsilon 4$ allele with physical inactivity on MMSE score (p for interaction < 0.05), but not with any other individual VRFs. The joint-effect analysis indicated that compared to those with no APOE $\epsilon 4$ allele or physical inactivity, individuals with either APOE $\epsilon 4$ allele or physical inactivity alone did not have a significantly lower MMSE score, but people having both APOE $\epsilon 4$ allele and physical inactivity had a markedly lower MMSE score in model 1 (β : -1.36, 95% CI: -2.58 to -0.15, $p < 0.05$) and model 2 (β : -1.33, 95% CI: -2.56 to -0.11, $p < 0.05$) (Fig. 1A).

There were statistical interactions of TOMM40 G allele with physical inactivity and diabetes (all p for interaction < 0.05), but no interaction with any other VRFs. The joint-effect analysis showed that compared to people with no TOMM40 G allele or physical inactivity, individuals with only TOMM40 G allele or only physical inactivity did not have a significantly lower MMSE score, but people having both TOMM40 G allele and physical inactivity had a markedly lower MMSE score in model 1 (β : -2.20, 95% CI: -3.38 to -1.01, $p < 0.001$) and model 2 (β : -2.12, 95% CI: -3.31 to -0.94, $p < 0.001$) (Fig. 1B). Compared to

people with no TOMM40 G allele or diabetes, individuals with diabetes alone, but not TOMM40 G allele alone, had a significant lower MMSE score (β : -1.15, 95% CI: -1.86 to -0.44, $p < 0.01$) and model 2 (β : -1.14, 95% CI: -1.85 to -0.43, $p < 0.01$), and people having both TOMM40 G allele and diabetes had a markedly lower MMSE scores in model 1 (β : -1.74, 95% CI: -2.98 to -0.50, $p < 0.01$) and model 2 (β : -1.83, 95% CI: -3.06 to -0.59, $p < 0.01$) (Fig. 1C).

Discussion

The primary aim of the current study was to investigate the associations of VRFs, APOE ϵ 4 allele, and TOMM40 G allele with global cognitive function in Chinese elderly, with a focus on potential interactions between VRFs and the susceptibility genes. We found that physical inactivity and diabetes were independently associated with poor global cognitive performance. Furthermore, we detected interactions of physical inactivity with APOE ϵ 4 allele and TOMM40 G allele on global cognitive function such that physical inactivity in combination with either APOE ϵ 4 allele or TOMM40 G allele was associated with markedly lower MMSE scores than having either factor alone. We also revealed an interaction of TOMM40 G allele with diabetes such that having both diabetes and TOMM40 G allele was associated with a markedly lower MMSE score. Finally, when four modifiable VRFs (i.e., current smoking, physical inactivity, high LDL-C, and diabetes) were aggregated, an increasing number of having these factors was associated with a decreasing MMSE score in a dose-response manner.

Associations of VRFs with global cognitive function

Most of the previous studies have focused on individual VRFs in association with cognitive function, in which the associations with some VRFs (e.g., hypertension, obesity, and high cholesterol) largely depend on the age when VRFs are assessed, i.e., having these factors in midlife or young-old age, but not necessarily in very old (e.g., age ≥ 80 years), was associated with cognitive impairment and dementia [29, 30]. Our study suggested that physical inactivity and diabetes were associated with poor cognitive performance, which is in line with the literature [31, 32]. Evidence has been accumulating that people who are exposed to multiple VRFs simultaneously often perform much worse on different cognitive tests [7, 33] and have a much higher risk of developing dementia than those who have a single VRF [34]. However, most of these studies are carried out in western countries. Our results extend prior work by showing that the greater vascular risk burden was associated with poorer global cognitive function among community-dwelling Chinese older adults. Notably, the vascular risk burden was based on all modifiable VRFs and included even some factors that were potentially (even not statistically) related to poor cognitive performance. This may imply that early preventive interventions targeting multiple modifiable VRFs simultaneously in cognitively normal older adults may be effective in slowing cognitive aging and delaying the onset of the dementia syndrome.

Associations of APOE ϵ 4 allele, TOMM40 G allele with cognitive function

In the current study, the APOE ϵ 4 allele is not associated with the MMSE score in Chinese older adults. Although some studies from western countries (e.g., Northern Europe) have found APOE ϵ 4-related decline in global cognitive function [35, 36], the population-based study failed to observe a significant association of APOE ϵ 4 allele with MMSE score in Chinese older adults [37]. Of note, compared to the proportion of people carrying APOE ϵ 4 allele in the Nordic population (around 25–30%), the proportion in our study is relatively low (14.9%), and only 1.4% carried the homozygote ϵ 4 allele. Thus, ethnic differences in genetic susceptibility may partially contribute to the discrepancy of research findings across studies. In addition, episodic memory and executive functioning are the cognitive domains to be particularly affected by carrying the ϵ 4 allele [38–40], global cognitive function may not be a sensitive measurement to APOE ϵ 4 allele.

Mitochondrial dysfunction is implicated in neurodegenerative disorders, such as AD. TOMM40 may have an effect on cognitive function in this regard by influencing downstream apoptotic processes within the mitochondrial system [41, 42]. Indeed, TOMM40 rs2075650 G, as the second most important risk allele in the APOE region, has been associated with AD [10, 43]. Recently, the TOMM40 G allele has also been associated with cognitive deterioration, but the association may vary depending on the study populations [11]. In the present study, we provided evidence that TOMM40 G allele was potentially associated with poor global cognitive performance. Further research is warranted to clarify the relationship of TOMM40 G with global cognitive function in Chinese older adults.

Interactions between VRFs and susceptibility genes

Our study extends the previous findings by revealing an interaction of APOE ϵ 4 allele and physical inactivity on global cognitive function among Chinese elderly. More interestingly, we detected the interactions of TOMM40 G with physical inactivity and diabetes on poor global cognitive function, which have not been reported previously. The interactive effects suggest that TOMM40 G carriers, if they are also physically inactive or if they have diabetes, will show substantially poor performance in global cognitive test. Although the biological mechanisms behind the gene-environment interactions are not fully understood, evidence has shown that APOE ϵ 4 allele may possibly interplay with VRFs to impair cognitive function, through influencing amyloid- β (A β) accumulation, lipid metabolism or brain structure [26, 44, 45]. Some studies have indicated that VRFs can accelerate cognitive decline by aggravating mitochondrial damage [46]. However, whether the TOMM40 gene exaggerates this association is unclear, and more research is needed to better understand the mechanisms. Our results provide evidence that interventions targeting unhealthy lifestyle (e.g., physical inactivity or sedentary lifestyle) and cardiovascular risk factors (e.g., diabetes) may be particularly effective for maintaining cognitive function among older carriers of susceptibility genes (e.g., TOMM40 G and APOE ϵ 4 alleles). Our main findings of gene-environment interactions deserve further investigation in different populations.

Strengths and limitations

The main strength of this study refers to the community-based design of older adults. However, limitations of our study deserve mentioning. First, we cannot determine the temporal and causal

relationships from a cross-sectional study, and the findings of any associations might be subject to bias due to selective survival. However, selective survival is likely to dilute the true associations given that exposures (VRFs and APOE ϵ 4 allele) and outcomes (poor cognitive performance) are known to be associated with mortality. Second, the study sample was relatively small, and thus may not have enough power to detect an association of those factors that have weakly-to-moderately strong associations with global cognitive function. Third, although MMSE is a validated and widely used test of global cognitive functioning with orientation, memory, attention-calculation, language, and registration components, it has also been argued that it does not tap into executive functions and psychomotor speed, the cognitive domains that are often impaired by exposures to VRFs and related cerebrovascular disease.

Conclusion

This community-based study provides evidence suggesting that modifiable VRFs and susceptibility genes (APOE ϵ 4 allele and TOMM40 G allele) are associated with poor cognitive function in Chinese older adults and that certain VRFs (e.g., physical inactivity and diabetes) and the genetic factors could have interactive effects on poor cognitive performance. While these results imply that interventions targeting those modifiable VRFs may help maintain cognitive function among older adults, especially among people carrying susceptibility genes, large-scale community-based longitudinal studies are still needed to further clarify the causal relationships between VRFs and cognitive function and their interactive effects with susceptibility genes on cognition.

Abbreviations

VRFs: Vascular risk factors; MMSE: Mini-Mental State Examination; APOE: Apolipoprotein E; TOMM40: Translocase of outer mitochondrial membrane 40; AD: Alzheimer's disease; SNPs: Single-nucleotide polymorphisms; GDS: Geriatric Depression Scale; BMI: Body mass index; TC: Total cholesterol; TG: Triglycerides; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; CI: Confidence interval

Declarations

Acknowledgments

Not applicable.

Author's contributions

WJG and JL developed the research question and designed the study. WJG analyzed the data and wrote the manuscript. JL is the principal investigator of this project. JL and CXQ supervised the study. JL and CXQ critically revised the paper. All authors approved the final version of the paper.

Founding

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Availability of data and materials

The data sets generated and analyzed during the current study are not available publicly as ethical clearance was not obtained to share data publicly. However, the data is available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Ethics Committee at the Institute of Psychology, Chinese Academy of Sciences, Beijing, China. Written informed consent was given by each participant at each visit.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Key Laboratory of Mental Health, Center on Aging Psychology, Institute of Psychology, Chinese Academy of Sciences, Beijing, China

²Department of Psychology, University of Chinese Academy of Sciences, Beijing, China

³Department of Neurology, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, Shandong, China

⁴Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet-Stockholm University, Stockholm, Sweden

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Figures

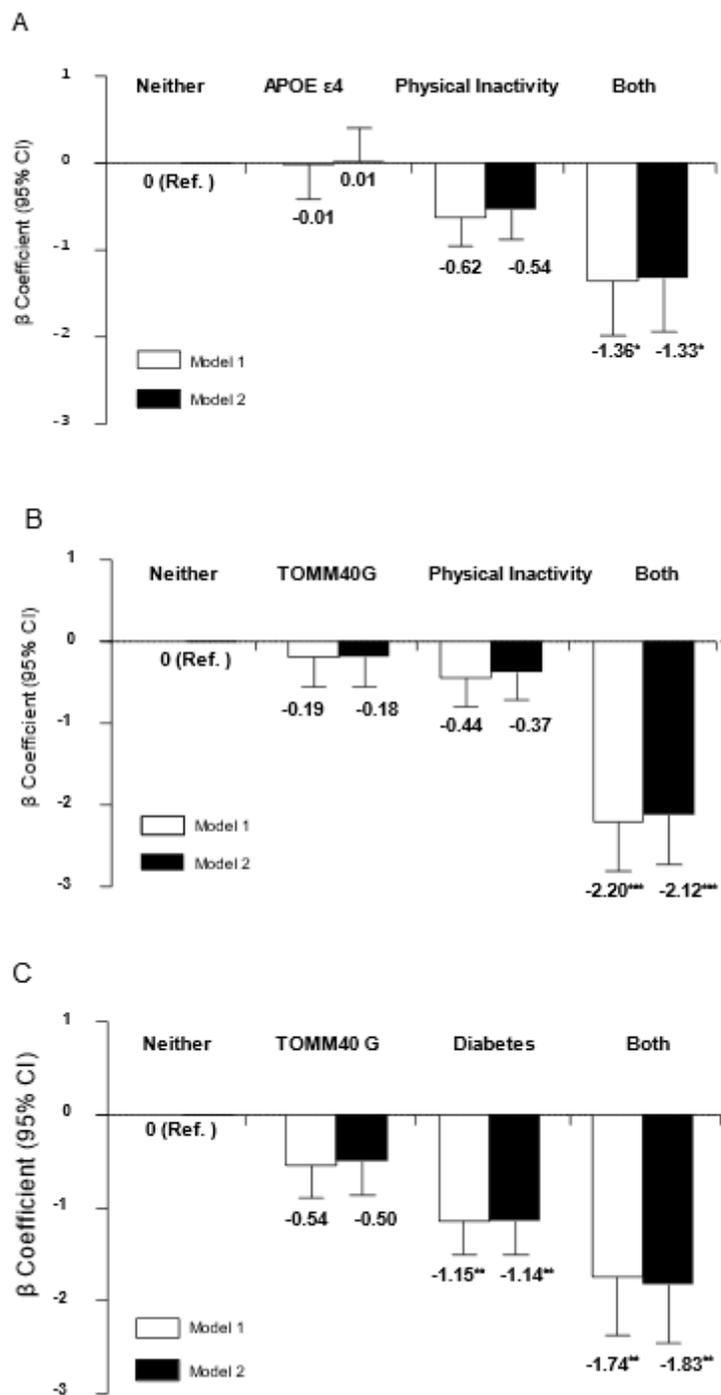


Figure 1

Joint effects of APOE ϵ 4 allele and physical inactivity (A), TOMM40 G allele and physical inactivity (B), and TOMM40 G allele and diabetes (C) on MMSE score. *p < .05; **p < .01; ***p < .001