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The interaction of obesity with susceptible gene polymorphisms in the relationship with mild cognitive impairment

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Abstract

Mild cognitive impairment (MCI) in the elderly is threatening the mental health of the elderly, and the interaction of some factors is worth exploring. This study aims to explore the interactions of obesity and gene polymorphisms in the relationship with MCI. A total of 2555 community resident dwellings include 444 participants who met MCI criteria recruited from the Ningxia province of China. Fourteen MCI-susceptible single nucleotide polymorphisms were detected using a high-throughput mass spectrometer. The interaction was examined by performing the multifactor dimensionality reduction model and unconditional logistic regression model. Logistic regression showed that obesity (*OR* = 1.42, 95%*CI*: 1.04–1.94), rs2075650G allele carrying (*OR* = 17.95, 95%*CI*: 1.32–244.95), rs11556505T allele carrying (*OR* = 0.06, 95%*CI*: 0.01–0.87) were statistically associated with MCI. Multifactor dimensionality reduction analysis showed a strong antagonistic effect between obesity and rs4402960 (Interaction dendrogram between obesity and rs4402960 is red) and a weak synergy effect on rs7901695 (Interaction dendrogram between obesity and rs7901695 is green). The hierarchical analysis showed obesity is a risk factor for MCI in the non-rs4402960T allele carrier group (*OR* = 1.55, 95%*CI*: 1.02–2.35). This study found that obesity is an independent risk factor for MCI, and the interactions with MCI-susceptible gene polymorphisms suggest a possible precision preventive intervention program should be developed to reduce the risk of MCI among individuals with obesity in the community.

Abbreviations: AD = Alzheimer disease, ADL = activities of daily living, APOE = apolipoprotein E, BMI = body mass index, DE7A = phosphodiesterase 7A, FPG = fasting plasma glucose, GDS = Geriatric Depression Scale, GWAS = Genome-Wide Association Studies, MCI = mild cognitive impairment, MDR = multifactor dimensionality reduction, MMSE = Mini-Mental State Exam, SNPs = single nucleotide polymorphisms, TOMM40 = The outer mitochondria membrane 40 homolog.

Keywords: case-control study, gene polymorphisms, interaction, mild cognitive impairment, obesity

1. Introduction

With the rapid global aging of the population, aging-related health issues including cognitive decline, mild cognitive impairment (MCI), and dementia have become crucial public health issues.[1] Approximately 47.5 million people worldwide have dementia which is predicted to nearly triple in size by 2050.[2] The number of dementia patients in China accounts for about 25% of the world total population of dementia.[3] At present, there is no clear and effective way to prevent and treat dementia. MCI has been regarded as a transitional stage between normal aging and dementia.[4] Its further development into Alzheimer disease (AD) and other dementias significantly increased.[5] A prospective cohort study showed that the conversion rate of MCI patients to AD is 10% to 12% per year, which is ten times higher than the incidence of AD in the normal population.[6] Thus, intervention with relevant measures at the stage of MCI can slow down or avoid the conversion of MCI to AD, and it is currently recognized as the best window period for preventing dementia.[7]

Studies have shown that the prevalence of MCI in Chinese older adults is ranged from 9.7% to 23.3%.[7,8] The pathological mechanism of MCI is complex and is affected by environmental factors and genetic factors.[9] The previous study suggests that obesity is one of the risk factors for MCI.[10] Overweighted and obsessed individuals had an increased risk of 0.7 times and 2.3 times in the middle-aged population.[11] Genome-Wide Association Studies (GWAS) have identified many susceptible

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single nucleotide polymorphisms (SNP) of multiple genes of MCI.[12] Previous studies have suggested that the apolipoprotein E (APOE) Ɛ4 allele accelerates Tau protein hyperphosphorylation and causes neurolipid metabolism to become impaired and affect cognitive function.[13] Phosphodiesterase 7A (PDE7A) gene expression products can affect cognitive function by regulating inflammation and oxidative damage.[14] The polymorphism of the outer mitochondria membrane 40 homolog (TOMM40) gene (rs11556505, rs2075650) is significantly associated with AD in Asians.[15] Clusterin gene polymorphism (rs9331888) is associated with β-amyloid (Amyloid β-protein) accumulation and hippocampal atrophy, which affects cognitive function.[16]

Unfortunately, at least currently, those genetic determinants are unchangeable. In the context of precision medicine, how to effectively intervene in genetic factors to reduce population susceptibility to diseases has become attractive in academic society. One possible strategy is analyzing the interaction between environmental factors and genes (E × G) and then intervening in corresponding changeable environmental factors to reduce population susceptibility. Several studies have provided primary evidence that supports the strategy of reducing the risk of disease susceptibility based on the E × G interaction. Studies have found that a low-fat diet or physical activities may reduce the risk of cardiovascular disease (one of the proximal determinants of MCI) among those who carry the APOE Ɛ4 gene (known as a high-risk allele of MCI).[17,18] Darteil et al found a lower risk of AD among Tibetans in part due to the effect of religiosity on genetic factors.[19] A previous study revealed that obesity significantly interacted with rs6006611 in association with nonalcoholic fatty liver disease among a Chinese minority sample.[20] Additionally, studies have found that Corona Virus Disease 2019 worsened the performance of those with MCI-susceptible genes.[21] However, to the best of our knowledge, no study has yet examined the interaction of obesity with susceptible SNPs in association with MCI. The current study aims to explore the interactions between obesity and genes with MCI using a large community sample in China western area and provide references for exploring the precision prevention of MCI.

2. Methods

2.1. Participants and procedure

Participants in this study were enrolled from Ningxia province in mainland China. The health data and blood samples were collected between 2013 and 2016 during the routine health examination program.[22] Those aged 55 or over years with a resident registration are eligible to join the study. Exclusion criteria as individuals with a history of severe mental disorders; those who are unable to finish the cognitive function exam due to severe hearing, vision, and speech impairments; individuals unable to participate due to severe physical diseases (including severe cerebrovascular diseases). A total of 2845 participants agreed to provide blood samples and health information. Of them, 2555 finished SNPs detection were included in this study, missing value adopts the method of missing value interpolation. All subjects signed the informed consent form at the beginning of the study. This study was reviewed and supervised by the Biomedical Ethics Committee of Ningxia Medical University (NYLZ No. 2015-151, 2018-115).

2.2. Measurement

2.2.1. Neuropsychological testing and physical examination. All participants underwent a careful physical examination at a health care center to obtain the blood sample. Trained attending physicians hired to perform neuropsychological testing by face-to-face interview. One item question: "Do you have significant memory decline recently?" asked to identify self-report memory complaints. The Chinese version Mini-Mental State Exam (MMSE),[23] activities of daily living (ADL) scale,[24] and the Geriatric Depression Scale (GDS) were administered at that time.[25] Research results have shown that the MMSE scale has good consistency among different research subjects, with an intra-group correlation coefficient (ICC) of 0.97 and a retest reliability of 0.80 to 0.99.[26] The GDS was found to be an internally consistent measure with Cronbach Alpha, split-half coefficients and test-retest reliability were 0.9, 0.89, and 0.58 respectively.[27] The ADL scale demonstrates good psychometric properties in varied populations, Cronbach alpha is 0.82 and intra-group correlation coefficients is 0.86 in community older adults.[28] MCI was assessed depending on a modified Peterson criteria,[7] which take the educational attainment into account when evaluating the MMSE scores as follows: MMSE ≤ 17 for those with no formal education; MMSE ≤ 20 for those with primary school education (≥6 years); and MMSE ≤ 24 for those with junior high school education or above (≥9 years).

2.2.2. Measurement of obesity. Body mass index (BMI) was calculated using the equation: BMI = body mass (kg)/height $(m)^2$, of which height and weight measurements were obtained from individuals by utilizing a disposable measuring tape. Obesity is defined as a BMI ≥ 28 kg/m^2.[29]

2.2.3. Demographical variables. Demographic characteristics, including age, gender, living situation (living alone or not), and educational attainment (illiterate, primary school, junior school, senior school, and over) were collected using a standard questionnaire. Participants with fasting plasma glucose (FPG) levels over 6.2 mmol/L were considered abnormal.[30] FPG was detected using an automatic biochemical analyzer (Hitachi 7180 automatic biochemical analyzer, Japan).

2.2.4. Gene polymorphism test. By reviewing the literature, screening GWAS studies related to MCI, dementia, and cognitive decline with a sample size greater than or equal to 1000 from 2010 to 2018, including SNPs that suggest significant significance related to MCI. A total of 14 susceptibility gene loci were included in this study: rs7412, rs429358, rs10808746, rs11556505, rs2075650, rs2143571, rs2896019, rs4402960, rs6006611, rs738409, rs7901695, rs9331888, rs985421, rs9877502. The primers are designed using Agena Bioscience ADS2.0 software, and a high-throughput mass spectrometer (MassARRAY Analyzer 4 System) is used for detection. MassARRAY TM RT software is used to analyze the quality and typing of samples. Huada Genetic Testing Company completes all tests according to standard procedures. The basic process of the experiment: Experimental design and primer synthesis: The company is responsible for the design and synthesis, and then the quality of the primers and the adjustment of the primer reaction concentration are carried out. Experimental procedure: polymerase chain reaction amplification; Shrimp Alkaline Phosphatase enzyme treatment to degrade the dNTP used for amplification to ensure that only 1 base is extended in the extension reaction; Single base extension reaction of extension primers; Resin desalting purification; Nanodispenser SpectroCHIP chip spotting; MassARRAY Analyzer Compac mass spectrometry detection. TYPER4.0 software analyzes the experimental results and obtains typing data. The genotype and allele frequency of each group were calculated according to the genotype of the research object, and the Hardy-Weinberg genetic balance test used the χ^2 test.

2.3. Statistical analysis

Statistical analysis was performed under the Social Science Statistical Package version 23.0. software (IBM, NC, USA). The mean substitution method was used to replace missing values in

the scale measure, and the means replace method was used for continuous variables when missing values were <20%. Means and standard deviations were used to describe continuous variables, and counts and proportions were used to describe categorical variables. The results of unconditional logistic regression analysis controlled for age, gender, education level, whether to live alone, times of marriage, and physical health conditions. The interaction analysis uses the multifactor dimensionality reduction (MDR) model[30] to detect the possible interaction between obesity and gene polymorphisms.[31] According to the best model determined in the MDR analysis, the logistic regression model is used to estimate the OR for interaction depending on the best model. The Hardy-Weinberg equilibrium test was conducted using Chi-squared test (APOE:$\chi^2 = 0.49$, $P > .05$; rs10808746:$\chi^2 = 0.68$: $P = .194$; rs2075650:χ^2 =0.07, $P = .798$; rs2143471:$\chi^2 = 0.35$, $P = .650$; rs2896019:$\chi^2 = 0.20$, $P = .651$; rs6006611: $\chi^2 = 1.64$, $P = .200$; rs738409:$\chi^2 = 0.68$, $P = .409$; rs7901695:$\chi^2 = 3.98$, $P = .045$; rs9331888:$\chi^2 = 0.01$, $P = .978$; rs985421:$\chi^2 = 0.08$, $P = .783$; rs9877502:$\chi^2 = 0.36$, $P = .550$).

3. Results

3.1. Demographic characteristics of participants

444 participants out of 2555 participants met the criteria of MCI, as shown in Table 1, participants with MCI had an older age (66.03 ± 6.33 vs 64.00 ± 5.25 years, $P < .001$), higher ADL score, and higher GDS score than the control group. In total, 400 participants met obesity criteria with a detection rate of 15.7% (400/2555), and the proportion of obesity in the MCI group was slightly greater than that in the control group (17.8% vs 15.3%, $P = .075$). There were statistical differences between the MCI group and the non-MCI group in gender, education level, times of marriage, and nonalcoholic fatty liver ($P < .01$). There was no statistical difference in living alone, hypertension, and abnormal fasting blood glucose ($P > .05$).

3.2. Univariate association between susceptible SNPs and MCI

As shown in Table 2, statistically significant differences were found in genotype frequencies between cases and control subjects for the 10808746, rs11556505, rs4402960, rs6006611, and rs7901695 ($P < .05$). The genotype frequency distribution of the 3 genotypes A/A, G/A, and G/G of rs9877502, G/G, G/T, and T/T of rs2896019 are statistically different between the MCI group and the non-MCI group ($P < .05$).

3.3. Multivariate unconditional logistic regression analysis

As shown in Table 3, after controlling for the covariates, obesity is an independent risk factor for MCI (*OR* = 1.42, *CI*95%: 1.04–1.94), rs11556505T allele carrying is an independent protective factor for MCI (*OR* = 0.06, *CI*95%: 0.01–0.87), and rs2075650G allele carrying is an independent risk factor for MCI (*OR* = 17.95, *CI*95%: 1.32–244.95).

3.4. Interaction among gene variants and obesity

As the MDR analysis showed (Fig. 1), the best model identified as obesity, rs7901695 and rs4402960 (cross-validation consistency and the prediction error obtained from MDR analysis are: CVC = 8/10, training accuracy = 0.563, testing accuracy = 0.552). The interaction dendrogram (Fig. 2) demonstrates that obesity has a strong antagonistic effect on rs4402960 (Interaction dendrogram between obesity and rs4402960 is red) and a weak synergy effect on rs7901695 (Interaction dendrogram between obesity and rs7901695 is green).

3.5. Unconditional logistic regression analysis stratified by rs4402960T

As shown in Table 4, after controlling for general demographic data (education level, living alone, marital status) and physical health status (fasting blood sugar, blood pressure, nonalcoholic fatty liver), the results showed that in the rs4402960T allele carrier group, obesity was not associated with MCI (*P*0.05). While in the non-rs4402960T allele carrier group, obesity is a risk factor for MCI (*OR* = 1.55, 95%*CI*: 1.02–2.35).

4. Discussion

In this study, we found obesity is an independent risk factor for MCI, rs11556505 is an independent protective factor of MCI,

Table 1

Univariate association between socio-demographic variables and MCI, n (%).

Variables	Total n = 2555	MCI n = 444	Non-MCI n = 2111	$\chi 2/t$	*P* value
Age, mean (SD), yr	64.35 (5.50)	66.03 (6.33)	64.00 (5.25)	7.13	<.001
ADL, mean (SD)	15.24 ± 3.37	17.05 ± 5.69	14.87 ± 2.67	9.81	<.001
GDS, mean (SD)	5.51 ± 5.69	6.60 ± 6.09	5.28 ± 5.55	4.37	<.001
Gender, male	1201 (47.0)	243 (54.7)	958 (45.4)	53.35	<.001
Education				21.79	<.001
Illiterate	1283 (50.2)	258 (58.1)	1025 (48.6)		
Primary school	649 (25.4)	93 (20.9)	556 (26.3)		
Junior school	387 (15.1)	71 (16.0)	316 (15.0)		
Senior school	236 (9.2)	22 (5.0)	214 (10.1)		
Living alone	330 (12.9)	64 (14.4)	266 (12.6)	1.07	.300
Marriage times				6.94	.031
Once	2464 (96.4)	422 (95.0)	2042 (96.7)		
Twice	91 (3.6)	22 (5.0)	69 (3.3)		
Hypertension	1593 (62.3)	261 (58.8)	1332 (63.1)	0.28	.598
Obesity, yes	400 (15.7)	79 (17.8)	321 (15.2)	3.17	.075
FPG, >6.2, mmol/L	361 (14.1)	59 (13.3)	302 (14.3)	0.08	.799
NAFLD, yes	522 (20.4)	71 (16.0)	451(21.4)	4.59	.032

Allele and genotype distribution of SNPs.

ADL = activities of daily living, FPG = fasting plasma glucose, GDS = Geriatric Depression Scale, MCI = mild cognitive impairment, NAFLD = nonalcoholic fatty liver disease, SNP = single nucleotide polymorphisms.

Table 2

Univariate association between susceptible SNPs and MCI (n = 2555).

SNPs	Sample	N	Geno-type						χ^2	*P*	allele		χ^2	*P*	*OR* (95%*CI*)
APO E			ε3/ε3	ε4/ε4	ε3/ε4	ε3/ε2	ε2/ε2	ε2/ε4			ε4	ε3/ε2			
	MCI	426	46	5	64	301	4	6	2.86	0.722	80	772	0.02	.902	0.98 (0.76–1.27)
	Non-MCI	2047	263	23	325	1391	26	19			390	3704			
rs9331888			C/C	C/G	G/G						G	C			
	MCI	444	124	227	93				0.77	0.856	413	475	0.28	.600	1.04 (0.90–1.20)
	Non-MCI	2110	626	1046	438						1922	2298			
rs10808746			G/G	G/A	A/A						A	G	94.92	<.001	2.06 (1.78–2.39)
	MCI	443	77	211	155				0.12	0.990	521	365			
	Non-MCI	2105	749	989	367						1723	2487			
rs11556505			CC	TC	TT						C	T			
	MCI	441	359	82	0				1.92	0.751	441	82	16.45	<.001	0.59 (0.46–0.76)
	Non-MCI	2094	1680	407	7						3767	414			
rs985421			G/G	G/A	A/A						G	A			
	MCI	444	312	122	10				1.96	0.376	746	142	1.73	.189	1.14 (0.94–1.39)
	Non-MCI	2111	1427	615	69						3469	753			
rs9877502			G/G	G/A	A/A						G	A			
	MCI	363	180	165	18				11.87	0.018	525	201	2.53	.112	1.16 (0.97–1.38)
	Non-MCI	1794	868	752	174						2488	1100			
rs2076650			G/G	G/A	A/A						G	A			
	MCI	444	2	81	361				2.81	0.422	85	803	1.28	.258	0.87 (0.68–1.11)
	Non-MCI	2009	26	406	1677						458	3760			
rs2143571			G/G	G/A	A/A						G	A			
	MCI	443	177	198	68				7.20	0.066	552	334	2.36	.125	0.89 (0.77–1.03)
	Non-MCI	2111	906	933	272						2745	1477			
rs2896019			GG	GT	TT						G	T			
	MCI	442	76	193	173				15.16	0.002	345	539	3.62	.057	1.16 (0.99–1.34)
	Non-MCI	2111	273	959	879						1505	2717			
rs4402960			GG	GT	TT						G	T			
	MCI	443	258	154	31				2.32	0.509	670	216	100.25	<.001	0.40 (0.33–0.48)
	Non-MCI	2009	1300	675	134						3275	422			
rs6006611			G/G	G/A	A/A						G	A			
	MCI	443	119	227	97				7.18	0.066	465	1220	252.33	<.001	0.38 (0.33–0.43)
	Non-MCI	2111	549	1026	536						2124	2098			
rs738409			CC	CG	GG						C	G			
	MCI	444	179	194	71				2.79	0.426	552	336	1.32	.25	0.92 (0.79–1.06)
	Non-MCI	2009	878	952	279						2708	1510			
rs7901695			CC	TC	TT						C	T			
	MCI	444	0	48	396				3.08	0.380	96	840	29.83	<.001	1.98 (1.54–2.54)
	Non-MCI	2009	11	208	1890						230	3988			

95%CI =95% confidence interval, FPG =fasting plasma glucose, MCI = mild cognitive impairment, NAFLD = nonalcoholic fatty liver disease, OR =odds ratio, SE =standard error, SNP = single nucleotide polymorphisms.

and rs2075650 is the independent risk factor of MCI after controlling for covariates. In addition, we also explored that age and gender are also influencing factors of MCI. Further analysis under MDR revealed complex interactions between obesity and genes, a strong antagonistic effect on rs4402960, and a weak synergy effect on rs7901695 were identified. Those findings provide primary evidence to support that a possible precision preventive intervention program should be developed to reduce the risk of MCI among individuals with obesity in the community.

A multifaceted combination of risk factors is associated with chronic disease. Scientific literature has shown the association among individual and environmental factors with hypertension.[32] Obesity is closely related to the risk of cardiovascular complications, diabetes, and hypertension, and it damages the brain by affecting the chemical and risk factors associated with pathological neurodegeneration.[33] This study found that obesity is significantly related to the risk of MCI, which is consistent with the conclusions of many previous studies.[34,35] Previous studies have suggested that obesity in old age is significantly related to brain volume changes. It reduces brain volume through the progressive cerebrovascular process leading to stroke and infarction, which will lead to a slight cognitive decline.[36] The risk of cognitive impairment increases in older adults with subjective cognitive impairment. In a study, MCI prevalence was 6.7% for ages 60 to 64, 8.4% for 65 to 69, 10.1% for 70 to 74, 14.8% for 75 to 79, and 25.2% for 80 to 84.[37] Aging affects several brain regions, including the hippocampus, a region key for memory that is affected by cognitive decline in old age as well as AD.[38] Previous studies have shown that reported an increased risk of subjective cognitive impairment in female participants and those with older age and lower education level, this may be related to different rates of decline in bodily functions and lifestyle.[39]

Previous research results showed that obesity is a potential risk factor for amnestic MCI in the elderly,[40] and its association has significant differences between diverse populations. For example, among non-Hispanic Americans, people with obesity are 2.34 times more likely to develop MCI than normal or underweight people. In contrast, in Hispanics, underweight or normal individuals are 3.57 times more likely to develop MCI than people with obesity,[41] which suggests that obesity may interact with genetic factors. This study provides further evidence that obesity, as a changeable environmental determinant, may increase the risk of MCI by modifying the risk genes among Chinese older adults. Those findings are also consistent with the previous study that revealed that people who carry the APOEε4 gene and consume high-fat foods have a higher cardiovascular disease rate.[42]

In this study, the MDR results suggest that there is a strong interaction between obesity and the SNP locus rs4402960

Table 3

Multivariate analysis of the predictors of MCI (N = 2555).

Variable	β	*SE*	*χ2*	*P*	*OR* (95%*CI*)
Age	0.07	0.01	36.48	<.001	1.07 (1.05–1.09)
Gender	-0.77	0.14	31.39	<.001	0.46 (0.35–0.61)
Education	-0.04	0.07	0.30	.589	0.97 (0.85–1.10)
Living alone	-0.16	0.17	0.89	.347	0.85 (0.61–1.19)
Marriage times	0.42	0.30	2.00	.157	1.54 (0.85–2.79)
FPG, >6.1 mmol/L	-0.10	0.17	0.34	.558	0.91 (0.66–1.25)
Hypertension	-0.11	0.14	0.68	.409	0.89 (0.69–1.17)
NAFLD	-0.35	0.16	5.02	.025	0.71 (0.52–0.96)
Obesity	0.35	0.16	4.98	.025	1.42 (1.05–1.94)
APOEε4	0.04	0.23	0.02	.880	1.04 (0.66–1.64)
APOEε2	-0.22	0.18	1.52	.218	0.80 (0.56–1.14)
rs10808746G	0.05	0.13	0.13	.724	1.05 (0.82–1.34)
rs11556505T	-2.77	1.34	4.28	.038	0.06 (0.01–0.86)
rs2075650G	2.93	1.34	4.80	.028	18.69 (1.36–256.64)
rs2143571A	0.02	0.25	0.01	.948	1.02(0.62–1.66)
rs2896019G	-0.33	0.41	0.63	.427	0.72 (0.32–1.62)
rs4402960T	-0.23	0.12	3.51	.061	0.80 (0.63–1.01)
rs6006611G	-0.14	0.17	0.71	.401	0.87 (0.62–1.21)
rs738409G	0.24	0.36	0.47	.493	1.28 (0.64–2.56)
rs7901695C	-0.05	0.20	0.07	.795	0.95 (0.65–1.40)
rs9331888G	-0.10	0.13	0.56	.456	0.91(0.70–1.18)
rs985421A	0.24	0.13	3.22	.073	1.27 (0.98–1.65)
rs9877502A	0.10	0.12	0.64	.424	1.10 (0.87–1.40)

95%CI = 95% confidence interval, OR = odds ratio, SE = standard error.

APOE = apolipoprotein E, FPG = fasting plasma glucose, MCI = mild cognitive impairment, NAFLD = nonalcoholic fatty liver disease.

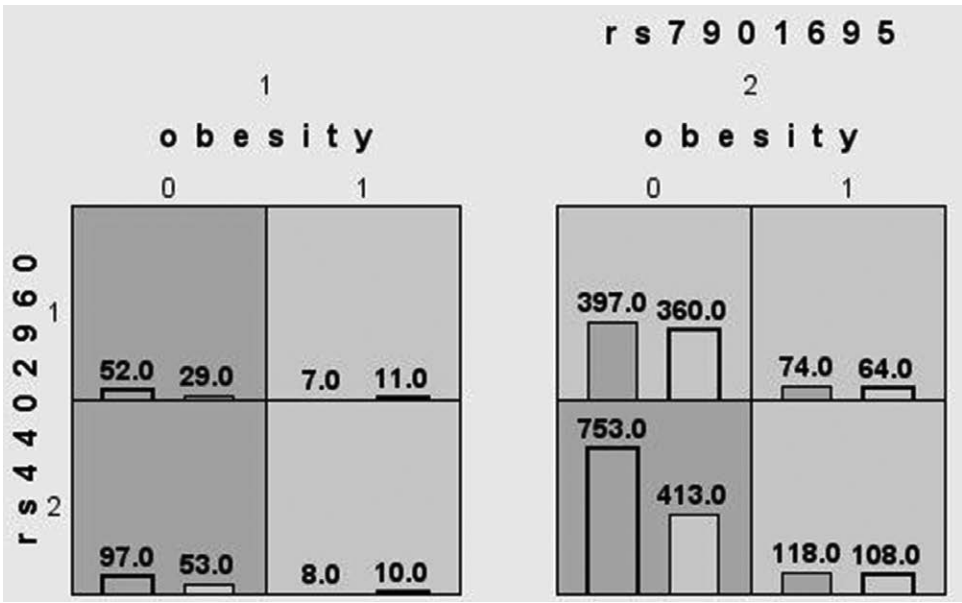

Figure 1. Distribution of high-risk (darker) and low-risk (lighter) factors in the best model (obesity, rs7901695, and rs4402960). The left bars within each box represented the case, while the right bars represented control. The heights of the bars are proportional to the sum of samples in each group. Note: obesity:0 = no, 1 = yes; rs7901695: 1 = Non-C allele carry, 2 = C allele carry; rs4402960: 1 = Non-T allele carry, 2 = T allele carry.

Figure 2. Interaction dendrogram between obesity, rs7901695, and rs4402960. The red line represented a strong antagonistic effect, and the green line represented a weaker synergy interaction.

Table 4

Unconditional logistic regression analysis stratified by rs4402960T Allele Carrier.

Variable	β	*SE*	*χ2*	*P*	*OR (95%CI)*
rs4402960T allele carrier (n = 400)					
Age	0.06	0.02	15.76	<0.001	1.06 (1.03–1.10)
Gender	-0.70	0.19	12.95	<0.001	0.50 (0.34–0.73)
Education	0.03	0.09	0.10	0.749	1.03 (0.86–1.23)
Living alone	-0.01	0.24	0.01	0.993	0.99 (0.62–1.60)
Marriage times	0.66	0.41	2.67	0.103	1.94 (0.88–4.30)
FPG	-0.07	0.23	0.10	0.755	0.93(0.60–1.46)
Hypertension	0.17	0.20	0.72	0.396	1.19 (0.80–1.77)
NAFLD	-0.24	0.22	1.23	0.268	0.79 (0.51–1.20)
Obesity	0.22	0.23	0.85	0.357	1.24 (0.79–1.96)
rs7901695	-0.25	0.27	0.86	0.354	0.78 (0.47–1.32)
Non rs4402960T allele carrier (n = 2155)					
Age	0.06	0.02	17.19	<0.001	1.07(1.03–1.10)
Gender	-0.80	0.19	17.18	<0.001	0.45 (0.31–0.67)
Education	0.10	0.09	1.15	0.284	0.91 (0.76–1.09)
Living alone	-0.33	0.25	1.70	0.192	0.72 (0.44–1.18)
Marriage times	0.17	0.47	0.13	0.722	1.18 (0.47–2.96)
FPG	-0.08	0.24	0.12	0.731	0.92 (0.58–1.47)
Hypertension	-0.33	0.18	3.21	0.073	0.72 (0.50–1.03)
NAFLD	-0.39	0.22	3.17	0.075	0.67 (0.44–1.04)
Obesity	0.44	0.21	4.14	0.042	1.55 (1.02–2.35)
rs7901695	0.15	0.29	0.28	0.598	1.17 (0.66–2.05)

95%CI = 95% confidence interval, FPG = fasting plasma glucose, NAFLD = nonalcoholic fatty liver disease, OR = odds ratio, SE = standard error.

of the insulin-like growth factor 2 binding protein 2 gene. When the regression model stratified by whether to carry the rs4402960T allele, there is no association between obesity and MCI found in the rs4402960T allele carrier group, and obesity in the non-rs4402960T allele carrier group is a risk factor for MCI. Obesity can cause insulin resistance in the surrounding tissues and central nervous system, especially the brain. Insulin resistance in the hippocampus leads to decreased neuroplasticity and impaired cognitive function.[34] A study has shown that insulin-like growth factor 2 binding protein 2 gene mutations can cause the function of pancreatic islet B cells to decline and reduce the insulin resistance caused by obesity.[43] However, no studies have reported an association between rs4402960 and cognitive decline. This is the first study report that rs4402960 polymorphism may be associated with MCI through interaction with obesity to the best of our knowledge.

Several previous GWAS studies have identified multiple susceptible SNPs related to MCI.[12,44,45] This study found that the TOMM40 gene, located upstream of the APOE gene, can form a channel for importing proteins into mitochondria in the outer mitochondrial membrane and affecting mitochondrial division, which is significantly associated with MCI among older Chinese. A study has shown that the rs11556505 allele T of the TOMM40 gene is a protective gene for MCI[46], it consistent with the results of this study. The abnormal expression of TOMM40 will directly affect the import function of mitochondrial proteins, resulting in the transmission of nuclear-encoded proteins to mitochondria being blocked and ultimately leading to mitochondrial dysfunction in the brain.[47,48]

Given the high prevalence of MCI and obesity in the Chinese population,[49] the present findings have value for understanding the mechanisms by which MCI develops. This finding of the interaction between gene and environmental predictors may be useful for others to build further research; these findings also provide a reference for health management institutions better to estimate the social burden of obesity on population health. It helps reveal the complex interactions between obesity and susceptible gene variants, and the results provide a theoretical basis for the precision prevention and treatment strategies for cognitive disorders. At the same time, targeted at high-risk or key populations with cognitive function decline and severe liver-related diseases, appropriate genetic polymorphism testing can be carried out, and effective intervention measures can be implemented early to achieve personalized prevention.

5. Limitations

This study has several limitations. First, the cross-sectional data collected provided less evidence of causal paths in the model, and even genetic exposure could be measured as an unchangeable variable. Second, due to the SNPs' weak effects on the outcomes, there may be a risk of failure to detect the potential association between the gene variants and MCI under the limited sample size. Furthermore, regarding feasibility, this study used a noninvasive method to evaluate the disease without considering the severity of MCI in the final data analysis, which may lead to information bias.

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