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ORIGINAL COMMUNICATION

Clinical predictors of cognitive decline in patients with mild cognitive impairment: the Chongqing aging study

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Abstract Mild cognitive impairment (MCI) is considered as the early stage of dementia which currently has no effective treatments. Reducing progression of cognitive decline at the MCI stage could be an important strategy for preventing conversion to dementia. The goal of this work was to screen for clinical predictors indicating the prognosis of MCI comprehensively; therefor, we assumed vascular risk factors (VRFs), carotid stenosis, and white matter changes (WMC) to be independent predictors. A total of 257 patients with MCI underwent collection of VRF information, neuropsychological evaluation, computed tomography angiography (CTA) to investigate carotid stenosis, and magnetic resonance imaging (MRI) to identify severity of WMC. After a 3-year follow-up period, the neuropsychological evaluation, CTA, and MRI were repeated to assess the progression of cognitive decline, carotid stenosis, and WMC. The conversion rate from MCI to dementia was 11.65% per year, and the conversion rate from MCI to Alzheimer's disease was 7.05% per year in our cohort. Cognitive decline (in terms of changes in Mini Mental State Examination scores) was associated with diabetes mellitus ($p = 0.004$), baseline WMC severity ($p < 0.001$), baseline carotid stenosis ($p < 0.001$), and WMC severity change ($p < 0.001$). Besides, diabetes, baseline WMC severity, baseline moderate-to-severe carotid stenosis, and carotid stenosis change during follow-up were predictors of conversion from MCI to dementia. Given the potential clinical predictors, our findings could imply that controlling blood glucose, removing carotid stenosis, and improving cerebral perfusion could be effective measures to delay cognitive decline in patients with MCI and prevent conversion from MCI to dementia.

Keywords Mild cognitive impairment (MCI) · Dementia · Vascular risk factors (VRFs) · Carotid stenosis · White matter changes (WMC)

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Introduction

Mild cognitive impairment (MCI) refers to an intermediate state of cognitive decline between the changes observed in aging and those fulfilling the criteria for dementia and often Alzheimer's disease (AD) [1]. More than half of patients with MCI progress to dementia within 5 years [2]. Thus, MCI can be regarded as an increased risk for progression to dementia, and its identification could lead to secondary prevention of dementia by controlling related somatic factors. Vascular risk factors (VRFs), such as hypertension [3, 4], diabetes [5, 6], hyperlipidemia [7, 8], and stroke [9, 10], play critical roles in the development of cognitive decline and AD among the treatable somatic factors [11]. However, there is still no certainty as to whether VRFs are simply additive elements compounding cognitive decline or whether they play a causal role by directly affecting cognitive impairment [12]. Most epidemiological studies have encountered difficulties in precisely gauging the role of VRF severity, and recent research has focused on identifying practical parameters which may precisely predict cognitive impairment. Indeed, chronic cerebral hypoperfusion (CCH) as a result of VRFs is a common vascular component among cognitive impairment risk factors

[13, 14]. Most studies investigating the possibility that CCH may predispose to reduced cognitive function have focused on carotid steno-occlusive disease [15, 16] and white matter changes (WMC) [17–19] in order to determine possible practical quantitative predictors of cognitive decline. However, there are relatively few reports which have assumed VRFs, carotid stenosis, and WMC to be the independent risk factors of cognitive decline in patients with MCI and which have explored the correlation between above factors and cognitive decline.

In this prospective study, our aim was to ascertain whether VRFs could be used to predict cognitive decline in an independent elderly cohort with MCI, taking into account carotid stenosis and WMC as two independent risk factors. We also aimed to identify the risk factors promoting conversion from MCI to dementia.

Methods

Study subjects

A total of 257 subjects were selected from inpatients in the Department of Neurology of Daping Hospital in the city of Chongqing during March–September 2008. Eligibility requirements included subjects (1) who were 60 years and older, (2) who were long-term residents of these communities, and (3) who were diagnosed as MCI. Exclusion criteria were (1) a diagnosis of dementia, or Hachinski Ischemic Score (HIS) $\leq$4 and HIS $\geq$7, (2) a concomitant neurologic disorder potentially affecting cognitive function (e.g., severe Parkinson's disease), (3) a history of stroke, (4) the degree of other cerebral arteriostenosis is greater than carotid stenosis, (5) being unable to comply with the study assessment, (6) enduring mental illness, or the score of Hamilton Depression Rating Scale (HDRS) >17, (7) drug abuse, (8) moving away or declining to participate. This study was approved by the Institutional Review Board of the Third Military Medical University, and all subjects and their caregivers provided informed consent.

Baseline data

These data included demographic data and VRFs.

Demographic data comprised age, sex, and educational level (lower educational level refers to the education time $\leq$6 years; higher educational level refers to the education time >6 years).

VRFs including hypertension, diabetes, hyperlipidemia, previous transient ischemic attack, and treatment were collected from a structured clinical interview (with caregivers' involvement), physical examination, and blood tests. Hypertension was defined as systolic blood pressure $\geq$140 mm Hg and/or diastolic blood pressure $\geq$90 mm Hg [20]. Diabetes was a concentration of fasting plasma glucose $\geq$7.0 mmol/l (126 mg/dl) [21], and hyperlipidemia was a total cholesterol concentration $\geq$5.2 mmol/l (200 mg/dl) and a low-density lipoprotein cholesterol concentration $\geq$3.4 mmol/l (130 mg/dl) [22]. These values were confirmed by repeated determinations before a definitive diagnosis was made. In addition, VRFs included smoking and drinking status. The smoking status was classified as follows: past smokers who had quit smoking for at least 6 months, current smokers, or nonsmokers. The drinking status was classified as drinking daily, weekly, monthly, occasionally, or never drinking previously as defined at the time the subjects were enrolled [23].

The treatment of VRFs included the following: use of diuretic, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, β-blocker, calcium channel blocker, or other antihypertensive medication for hypertension; oral antihyperglycemic or insulin for diabetes; statins for hyperlipidemia; smoking or drinking were considered "treated" if the patient ceased smoking or drinking during the follow-up period.

Neuropsychological evaluation

The cognitive and functional status was assessed using the Chinese version of the MMSE, Clinical Dementia Rating (CDR), and the Barthel Index of Activities of Daily Living (Barthel ADL Index), which had been previously validated in Chinese elderly people [23, 24]. The subjects with abnormal MMSE score were administered HDRS for measuring emotional status [25], and HIS for evaluating significant vascular disease [26]. Subsequently, a set of neuropsychological tests were applied, including Fuld Object Memory Evaluation (FOM) for detecting extensive cognitive dysfunction mainly composed of memory [27], Rapid Verbal Retrieve (RVR) for detecting the function of semantic memory [28], Wechsler Adult Intelligence Scale (WAIS) for evaluating immediate memory and function of graphical recognition [29], and the Pfeiffer Outpatient Disability Questionnaire (POD) for assessing ability of social activities [30]. We chose the MMSE to assess cognitive decline in this study because of its larger clinical application and high correlation with other indices such as ADAS-Cog which has been reported by Silvestrini et al. [31].

Diagnosis of MCI

The clinical diagnosis of MCI was made according to the established Petersen criteria [32], including (1) subjective complaint of memory deficits, (2) abnormal memory functioning for age (tests claim 1.5 SD below normative

values), (3) absence of dementia according to the diagnostic examination (MMSE ≥24 in subjects with higher educational level; MMSE ≥20 in subjects with lower educational level; CDR ≤0.5), (4) and normal everyday functioning on ADL (ADL >60). The subjects with a depressive disorder were excluded [33].

Diagnosis of dementia

Dementia was diagnosed based on criteria according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) [34]. Alzheimer's disease (AD), vascular dementia (VaD), and mixed dementia (MD) were all included. The diagnosis of AD was made according to the criteria for probable AD published by the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's disease and Related Disorders Association Work Group (NINCDS-ADRDA) [35]; the diagnosis of VaD was based on the criteria about probable vascular dementia published by the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) [36]; MD refers to Alzheimer's disease with cerebrovascular disease (CVD) which was diagnosed when the clinical picture of the subject presented aspects of both AD and VaD [37].

Diagnosis of cerebral arteriostenosis

The cerebral arteries were evaluated by means of CTA (Light Speed VCT 64-slice Scanner, General Electric, Milwaukee, WI), and the degree of cerebral arteriostenosis was assessed on an advanced workstation (Advantage 4.2, General Electric, Milwaukee, WI); the data were recorded, based on rounding (e.g., 0, 10, 20%). The final degree of carotid stenosis for each subject was defined as the maximum value of all sites of the common carotid arteries, carotid bulbs, and internal carotid arteries. The severity of carotid stenosis was grouped as mild (0–29%), moderate (30–69%), or severe (≥70%), according to the NASCET method [38].

Diagnosis of WMC

MRI was performed using a 3.0 T magnet (MAGNETOM Verio 3.0 T, Siemens) with T1- and T2-weighted and fluid-attenuated inversion recovery sequences (FLAIR) at entry and at the end of the study. The degree of WMC severity was rated on FLAIR by the practitioners in the department of radiology who were blind to the clinical data, using the three classes in the revised version of the visual scale of Fazekas and colleagues [39]. Taking into account only deep and subcortical white matter, lesions were classified into three categories: mild WMC (single lesions below 10 mm; areas of grouped lesions smaller than 20 mm in any diameter); moderate WMC (single lesions between 10 and 20 mm; areas of grouped lesions more than 20 mm in any diameter; no more than connecting bridges between individual lesions); or severe WMC (single lesions or confluent areas of hyperintensity 20 mm or more in any diameter) [40].

Follow-up

A total of 257 patients who were enrolled into the present study accepted follow-up for 3 years from 2008–2011. Demographic data and VRFs were collected at baseline. The same neuropsychological tests were administered at entry and at the end of follow-up by a neuropsychologist blinded to the medical records of the subjects. All subjects were examined by CTA and MRI at entry and at the end of follow-up. The type of CT machine, the software used to assess the degree of cerebral arteriostenosis, and the practitioners who assessed the WMC severity and were blinded to the cognitive status were kept the same at entry and at the end of follow-up. In addition, phone interviews were performed at 3-month intervals to obtain information concerning cognition status and check compliance.

Statistical analysis

A sample size calculation was performed briefly because this was an explorative study of possible risk factors for the progression of cognitive decline. According to baseline data, WMC severity, and carotid stenosis, the potential risk factors were less than 20; thus, 200 cases (20×10) would be the recommended sample size for a reliable analysis. Considering drop-outs, our final sample size was 257. Because this study aimed to explore clinical predictors for progression of cognitive decline (measured by a MMSE score decrease, a continuous variable, as dependent variable) related to WMC severity, carotid stenosis, and VRFs, our goal was best served by a linear regression model. Simple regression analyses were performed first to evaluate the bivariate association between MMSE decrease (subjects with stroke during follow-up were excluded for the confounding effect) and each potential predictor. Then the independent variables which had significant linear relevance with the MMSE decrease were entered into a multiple regression analysis; thus, some potential confounding effect of risk factors would be removed and a regression formula describing the MMSE decrease can be worked out. For those who converted to dementia (subjects with stroke during follow-up were included), we analyzed the difference between the dementia and subjects remaining in MCI by the *t* test for independent normally distributed

continuous data and the χ^2 test for categorical data. Then, the independent variables that were significantly different in the two groups were used to analyze the association for conversion to dementia by means of the Cox proportional hazard regression model. The statistical analyses were performed using SPSS 18.0 for Windows.

Results

A total of 257 subjects with MCI were enrolled into the study at baseline (mean age 70.05 years, SD 6.78; 43.19% women, 40.15% subjects with lower education level), 246 (95.72%) subjects completed the follow-up process, and only 11 (4.28%) subjects dropped out, 8 died and 3 declined. For these 11 subjects, no cognitive diagnosis was attributed. During follow-up, 36 subjects experienced a stroke, and these 36 subjects were excluded from linear regression. Considering the cognitive diagnosis performed at the last clinical visit, dementia was diagnosed in 86 (34.96%) subjects (among those who progressed to dementia, 60.47% progressed to AD, 30.23% to VaD, and 9.30% to MD). The conversion rate from MCI to dementia was 11.65% per year, and the conversion rate from MCI to AD was 7.05% per year which are similar to the values we previously reported and other investigations [32, 41]. The MMSE score decrease in subjects diagnosed with MD (9.00 ± 1.69) was larger than VaD (5.92 ± 2.45), and the smallest in subjects diagnosed with AD (5.58 ± 1.98).

Baseline characteristics

The baseline characteristics, including demographic data, VRFs and related treatments, WMC severity, and degree of carotid stenosis in 257 subjects, are presented in Table 1. MMSE scores exhibited a narrow baseline variability (coefficient of variation 6.16%), indicating that the sample had fairly homogeneous cognitive impairment. In this study, hypertension and previous transient ischemic attack were common; diabetes mellitus and hyperlipidemia were poorly treated. Mild WMC and moderate carotid stenosis were identified in a large proportion of patients.

Table 1 Baseline patient characteristics ($n = 257$)

Characteristics	Values
Demographic data	
Age, years, mean ± SD	70.05 ± 6.78
Female, *n* (%)	111 (43.19)
Lower education level (≤6 years), *n* (%)	103 (40.07)
VRFs of the study cohort, *n* (%)	
Hypertension	161 (62.64)
Diabetes mellitus	76 (29.57)
Hyperlipidemia	110 (42.80)
Previous transient ischemic attack	165 (64.20)
Antihypertensives	106 (41.24)
Oral antihyperglycemic or insulin	32 (12.45)
Statins	34 (13.23)
Daily drinking	54 (21.01)
Current smoking	55 (21.40)
Alcohol withdrawal	24 (9.34)
Smoking cessation	18 (7.00)
Cognition assessment	
MMSE score, mean ± SD	25.17 ± 1.55
WMC severity, *n* (%)	
None	44 (17.12)
Mild	110 (42.80)
Moderate	67 (26.07)
Severe	36 (14.01)
Carotid stenosis, *N* (%)	
Mild	113 (43.97)
Moderate	132 (51.36)
Severe	12 (4.67)

Effect of demographic characteristics, VRFs, WMC severity, and carotid stenosis on the 3-year decrease in MMSE

According to simple regression analysis (Table 2), the decrease of MMSE scores over the 3-year study period was mainly attributed to gender, diabetes mellitus, alcohol consumption, WMC severity, and degree of carotid stenosis at baseline and deterioration of WMC severity and carotid stenosis. Gender was related to the decreasing MMSE scores in the simple regression analysis because most of the male subjects reported smoking or drinking habits. We examined gender as a possible confounder and excluded it.

In addition, the decrease of the MMSE scores had to be adjusted for baseline cognitive status as well as age [23]. The adjusted decrease of the MMSE scores as a dependent variable and the above 6 risk factors as independent variables were entered into the main regression model (stepwise regression), which indicated that the MMSE score decrease was significantly related to diabetes mellitus ($p = 0.004$), baseline WMC severity ($p < 0.001$), baseline carotid stenosis ($p < 0.001$), and WMC severity change ($p < 0.001$) (Table 2, right side).

The MMSE score decrease can be described by the following formula: MMSE score decrease $= -1.180 + 1.611$ (baseline WMC severity) $+ 5.805$ (baseline carotid stenosis) $+ 1.221$ (WMC severity change) $+ 0.957$ (1 if with diabetes mellitus; 0 if without) ($F = 51.583$; $p < 0.001$; $R^2 = 0.674$).

Table 2 Regression of 3 years decrease in MMSE on demographic characteristics, VRFs, WMC severity and carotid stenosis ($n = 210$)

	Simple linear regression				Multiple linear regression			
	B	SE	*t*	*p* value	*B*	SE	*t*	*p* value
Gender (male vs. female)	0.728*	0.238*	3.057*	0.003*				
Age (years)	0.058	0.036	1.609	0.111				
Education level (years)	0.093	0.070	1.330	0.186				
Hypertension	0.675	0.499	1.353	0.179				
Antihypertensives	−0.360	0.498	−0.722	0.472				
Diabetes mellitus	1.679*	0.526*	3.192*	0.002*	0.957*	0.326*	2.934*	0.004*
Oral antihyperglycemic or insulin	1.332	0.829	1.606	0.111				
Hyperlipidemia	0.462	0.497	0.929	0.355				
Statins	−0.811	0.744	−1.090	0.278				
Previous TIA	0.356	0.504	0.707	0.481				
Alcohol consumption	1.297*	0.627*	2.068*	0.041*				
Alcohol withdrawal	0.709	0.926	0.765	0.446				
Smoking	0.655	0.613	1.068	0.288				
Smoking cessation	−1.020	0.983	−1.038	0.302				
Baseline MMSE score	−0.186	0.161	−1.146	0.254				
Baseline WMC severity	1.896*	0.207*	9.181*	0.000*	1.611*	0.182*	8.827*	0.000*
Baseline carotid stenosis	10.977*	1.479*	7.421*	0.000*	5.805*	1.213*	4.786*	0.000*
WMC severity change	1.141*	0.480*	2.377*	0.019*	1.221*	0.310*	3.933*	0.000*
Carotid stenosis change	6.310*	2.766*	2.282*	0.025*				

B = slope, SE = standard error of slope, $t = B$/SE

* With significant ($p < 0.05$) effect on MMSE change

Cox proportional hazards model with dementia at last clinical evaluation as a dependent variable

Using Cox proportional hazards model (Table 3; independent variables in Cox proportional model differed significantly between the subjects developing dementia and subjects remaining in MCI by means of a *t* test or χ^2 test; data not shown, available on request), it was found that diabetes, baseline WMC severity (severe), baseline carotid stenosis (moderate to severe), and carotid stenosis change during follow-up were predictors of conversion from MCI to dementia.

Cox proportional hazards model with AD at last clinical evaluation as a dependent variable

Using Cox proportional hazards model (Table 4), independent variables in this Cox proportional model did not include stroke during follow-up or severe carotid stenosis because the two conditions did not exist among the subjects who converted to AD. Finally, it was found that the predictors of conversion from MCI to AD were same as the result among subjects diagnosed as dementia except for carotid stenosis change during follow-up.

Discussion

AD is one of the most disabling and burdensome health conditions worldwide, but no effective treatment is available for the 4.6 million new patients who will be affected by AD this year [42]. Thus, it is of great importance to recognize and treat patients with MCI because this is an early stage of dementia [43] and is associated with an increased risk for progression to AD (10–15% per year), which is 10 times that in the normal population [32]. Most studies about MCI have pursued two goals: (1) to find the predictors which can indicate the prognosis of MCI and then recognize the patients with poor prognosis; (2) to identify the critical risk factors promoting the conversion from MCI to dementia. Thus, the identification of those patients with poor prognosis and subsequent management of critical risk factors at the MCI stage could be an important strategy for preventing and delaying progression to dementia.

The clinical predictors studies mainly focused people's attention on carotid atherosclerosis (carotid stenosis, plaque and intima-media thickness), WMC, and VRFs, such as hypertension and diabetes. In addition, VRFs have become the target of treatable risk factors [44, 45]. In the present prospective 3-year study, we enrolled 257 subjects

Table 3 Cox proportional hazards model, dependent variable: dementia at last clinical evaluation ($n = 86$)

	β	Hazard ratio	p	95% Confidence interval
Age	0.013	1.013	0.595	0.966–1.063
Education level	−0.727	0.484	0.083	0.212–1.101
Hypertension	−0.350	0.705	0.550	0.224–2.221
Diabetes mellitus	0.870*	2.387*	0.034*	1.069–5.333*
Antihypertensives	0.199	1.220	0.679	0.476–3.130
Oral antihyperglycemic or insulin	0.730	2.075	0.213	0.658–6.544
Baseline WMC severity			0.001*	
WMC severity (none vs. severe)	−15.019	0	0.935	0–3.0471E150
WMC severity (mild vs. severe)	−2.810*	0.060*	0.000*	0.018–0.202*
WMC severity (moderate vs. severe)	−0.796*	0.317*	0.047*	0.113–1.035*
Baseline carotid stenosis			0.004*	
Carotid stenosis (moderate vs. mild)	1.433*	4.190*	0.006*	1.517–11.572*
Carotid stenosis (severe vs. mild)	2.455*	11.641*	0.002*	2.496–54.292*
WMC severity change	0.622	1.863	0.115	0.859–4.040
Carotid stenosis change	5.069*	159.055*	0.005*	4.568–5,537.669*
Stroke during follow-up	0.614	1.848	0.110	0.871–3.922

* With significant ($p < 0.05$) effect on conversion from MCI to dementia

Table 4 Cox proportional hazards model, dependent variable: AD at last clinical evaluation ($n = 52$)

	β	Hazard ratio	p	95% Confidence interval
Age	0.49	1.050	0.133	0.985–1.119
Education level	−0.046	0.955	0.936	0.307–2.966
Hypertension	−0.291	0.747	0.723	0.150–3.733
Diabetes mellitus	1.072*	2.921*	0.028*	1.123–7.595*
Antihypertensives	−0.168	0.846	0.813	0.210–3.402
Oral antihyperglycemic or insulin	1.029	2.798	0.173	0.636–12.307
Baseline WMC severity			0.002*	
WMC severity (none vs. severe)	−14.496	0	0.962	0–1.894E253
WMC severity (mild vs. severe)	−3.280*	0.038*	0.001*	0.006–0.242*
WMC severity (moderate vs. severe)	−0.680	0.506	0.349	0.122–2.101
Baseline carotid stenosis			0.011*	
Carotid stenosis (moderate vs. mild)	2.135*	8.458*	0.003*	2.096–34.138*
WMC severity change	0.561	1.753	0.272	0.645–4.767
Carotid stenosis change	4.821	124.087	0.052	0.950–16,209.684

* With significant ($p < 0.05$) effect on conversion from MCI to AD

with MCI in Chongqing, the biggest municipality in southwest China. With the purpose of using advanced imaging technology and determining the practical clinical predictors comprehensively, we assumed VRFs, carotid stenosis, and WMC to be the independent risk factors of cognitive decline in patients with MCI in this study.

Our study showed that (1) in the present study, the conversion rate from MCI to dementia was 11.65% per year, and the conversion rate from MCI to AD was 7.05% per year. (2) After being adjusted for baseline cognitive status and age, cognitive decline of the patients with MCI during the 3-year follow-up were associated with diabetes, baseline WMC severity, baseline carotid stenosis, and WMC severity change; (3) among the subjects diagnosed as dementia at the end of follow-up, diabetes, baseline severe WMC, baseline moderate-to-severe carotid stenosis, and carotid stenosis change during follow-up were predictors of conversion from MCI to dementia; (4) among the subjects diagnosed as AD at the end of follow-up, predictors of conversion from MCI to AD were the same as those for subjects diagnosed with dementia except for carotid stenosis change during follow-up.

The predictors for MMSE score decrease, conversion from MCI to dementia, and conversion from MCI to AD were different in our study. However, diabetes, baseline WMC severity, and carotid stenosis were still identified as common predictors for every outcome of cognitive decline and all predictors for progression to AD. In addition to these common predictors, WMC severity change during follow-up was a predictor for the MMSE score decease, while carotid stenosis change during follow-up predicted progression to dementia. The differential results would be attributed to different populations, because subjects having a stroke during follow-up were excluded for the confounding effect when we analyzed the association factors of MMSE score decrease, while all subjects were included in Cox proportional hazards model with dementia and AD. We did not analyze predictors of progression to VaD and MD due to the limited number of subjects, but we could still infer a conclusion from the above results, i.e., carotid stenosis change during follow-up would mainly predict progression to VaD in addition to the common predictors of cognitive decline and WMC severity change during follow-up.

We previously found that hypertension, diabetes, and hypercholesterolemia were associated with a higher risk of incident AD dementia [41]. In this study, taking into account carotid stenosis and WMC in addition to VRFs, we found that diabetes was the only independent predictor of cognitive decline among all VRFs studied. The same result was reported in the LADIS study [40]. The Chinese people have paid more attention to hypertension during the recent 3 years, which can account for the discrepancy in our two studies. Controversial results have been published on the relationship between hypertension and dementia. Some studies suggested a higher incidence of dementia in patients with hypertension [4], but results of trials using antihypertensive medication have been inconclusive [40, 44]. Nevertheless, hypertension was not a predictor of cognitive decline during follow-up in our cohort, while diabetes was the only independent predictor of conversion from MCI to dementia among all VRFs studied.

Extracranial carotid Doppler ultrasound is commonly used to study carotid artery disease [46] due to its convenience and low price. However, it has limitations in evaluating the cerebral arteries more comprehensively; in fact, steno-occlusive disease of other cerebral arteries may be the confounding factor for the analysis of an association between carotid stenosis and cognitive decline. Therefore, we assessed cerebral arteries using CTA in order to exclude subjects with a higher degree of other cerebral arteriostenosis than carotid stenosis. After controlling for confounding factors, we found that moderate-to-severe carotid stenosis and deterioration of carotid stenosis are predictors of conversion from MCI to dementia.

WMC is considered as a manifestation of cerebral small vessel disease, which is one of the common causes of dementia [47]. Verdelho et al. [40] found that severe WMC at baseline was a predictor for cognitive decline in the LADIS sample40. A recent study reported that while progression of WMC was associated with progression for cognitive impairment and dementia, baseline, WMC measure was not [48]. In our findings, both baseline WMC severity and progression of WMC were associated with cognitive decline in patients with MCI, but just baseline WMC severity was a predictor of conversion from MCI to dementia.

The mechanism underpinning the association of VRFs, CVD, and cognitive impairment may mainly involve CCH [49, 50]. Various mechanisms of neuronal injury in CCH, including formation of free radicals, oxidative stress, mitochondrial dysfunction, inflammatory processes and apoptosis, have been proposed [51, 52]. These factors may interact and amplify each other, finally leading to clinical presentation of cognitive impairment. Cumulative animal experiment results have provided the evidence that altered Aβ metabolism appears to be a central initiating factor for cognitive impairment in animal models with CCH. Aβ peptides are generated from amyloid precursor protein (APP) by sequential actions of two proteolytic enzymes, the β-site APP cleavage enzyme 1 (BACE1) and the γ-secretase [53]. APP and BACE1 are both up-regulated in chronic cerebral hypoperfusion, and then the elevation of BACE1 contributing to APP processing and the increased APP lead to a high level of Aβ formation and eventual deposition [54]. Furthermore, the failure of Aβ clearance is a possible cause of Aβ deposition and amyloid plaque formation in CCH. Meanwhile, the formation of Aβ and accumulation in the vasculature may act to perpetuate further vascular dysfunction and accelerate white matter pathology [14], thus, forming a vicious cycle.

Our study is an observational study with inherent substantial limitations. We did not divide cognitive impairment or dementia into vascular and non-vascular type, because the focus of this study was cognitive decline. Carotid stenosis and WMC were selected to be candidates in our study because their assessments are more feasible than other types of cerebral atherosclerosis. With the aim of reducing bias induced by the impact of other cerebral atherosclerosis, we excluded subjects with higher degrees of other cerebral arteriostenosis than carotid stenosis. However, atherosclerosis is considered a systemic disease and we can not simplify the situation of the patient accurately. In addition, the propensity score and intention to treat analysis strategy used in our previous study were adopted in the present research, in order to reduce bias induced by changes in the VRFs and their treatment during follow-up [41]. Our findings indicate that carotid stenosis

change during follow-up is a predictor of conversion from MCI to dementia, but the threshold of carotid stenosis change still needs further research to be identified. Nevertheless, our study has implications for both clinical practice and research, emphasizing the need to identify patients with diabetes, severe WMC or moderate to severe carotid stenosis, but also the need to treat VRFs and carotid stenosis in order to prevent cognitive decline in patients with MCI.

Conflicts of interest None.

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