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Vascular Risk Factors and Mild Cognitive Impairment in the Elderly Population in Southwest China

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Abstract

Objectives: Increasing evidence has demonstrated that vascular risk factors (VRFs) contribute to cognitive impairment in the elderly population. Prevention and administration of VRFs can be a vital strategy for delaying cognitive impairment. This study aimed to determine the impact of VRFs on cognitive function of the aged people from Chongqing, Southwest China. **Methods:** A total of 597 participants ($\geq$60 years) from hospital and community population were enrolled in the cross-sectional study. Participants were screened for hypertension, coronary heart disease (CHD), and cerebrovascular disease (CVD). Blood pressure (BP) and blood lipid were also measured. Cognitive function was assessed with Mini-Mental State Examination and Clinical Dementia Rating. Logistic regression analysis was used to look for VRFs impacting mild cognitive impairment (MCI). Then we investigated the relationship between different types of vascular diseases and MCI. **Results:** A total of 457 participants showed normal cognitive function and 140 participants showed MCI. After adjusting for age, gender, and education, logistic regression analysis demonstrated that hypertension, CHD, systolic BP, total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) were independently associated with MCI; however, CVD, diastolic BP, triglyceride, and high-density lipoprotein cholesterol were not associated with MCI. Moreover, vascular diseases significantly contributed to MCI compared with no vascular disease; however, no significant difference in incident MCI was found among different combinations of vascular diseases. **Conclusions:** Hypertension, CHD, TC, and LDL-C are independent risk factors for MCI. Moreover, patients with vascular diseases have a higher risk of MCI; however, the amount of vascular diseases does not increase the risk of MCI.

Keywords

vascular risk factors, hypertension, coronary heart disease, cerebrovascular disease, dyslipidemia, mild cognitive impairment

Introduction

Cognitive impairment is a progressive condition from mild cognitive impairment (MCI) to dementia. Mild cognitive impairment, an intermediate state between normal cognitive (NC) function and dementia, is a common clinical manifestation affecting the aged people. It is suggested in large sample studies that the progression rates from MCI to dementia range between 5.4% and 11.7% per year; moreover, patients with MCI have higher risks of progression to dementia compared with healthy aging people.[1,2] At present, dementia is very common in the elderly population, and the number of people affected by dementia is continually increasing. It is estimated that to date more than 20 million people have dementia, and the total prevalence of dementia is predicted to quadruple by 2040.[3] However, there are no modifying treatments for dementia so far. The early intervention of cognitive impairment appears to be very important for the prevention of dementia.

Cerebral hypoperfusion can induce hypoxia/ischemia and contribute to structural and functional changes in the brain, which ultimately leads to cognitive impairment.[4,5] Multiple vascular diseases can lead to cerebral hypoperfusion, including hypertension, coronary heart disease (CHD), and cerebrovascular disease (CVD). Therefore, those vascular risk factors (VRFs) could be risk factors for cognitive impairment. Moreover, it is

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suggested that these VRFs are associated with the progression of dementia such as Alzheimer's disease (AD) and vascular dementia (VD).[6-9] Meanwhile, some studies also demonstrate that the treatment of VRFs can delay the onset and progression of cognitive impairment and dementia.[10] However, till date there is still no final conclusion about the relations between VRFs and MCI, based on published data.[11,12] Moreover, data on the correlation between VRFs and MCI are still lacking for Chinese population. Therefore, this issue needs to be further investigated in China because of race and regional differences.

The present study aimed to investigate the association of MCI with several VRFs, including hypertension, dyslipidemia, CHD, and CVD, in the elderly population in Chongqing, Southwest region of China, based on comprehensive geriatric assessment (CGA).

Methods

Study Participants

Hospital-based participants were recruited from Department of Geriatrics, The First Affiliated Hospital of Chongqing Medical University. Community-based individuals volunteered from clinic of community service center, Jiangbei District, Chongqing. Our study was performed from September 2011 to August 2012. Study participant's inclusion criteria were as follows: (1) 60 years and older; (2) no history of neuropsychiatric disorders; (3) no evidence of neoplastic diseases; and (4) agree to participate in the study. Exclusion criteria were as follows: (1) acute stress state; (2) diagnosed with dementia; (3) severe organ dysfunction; and (4) the participant or the relatives refused to participate in the study. The cognitive and functional status of all patients was assessed by using Mini-Mental State Examination and Clinical Dementia Rating (CDR), and recruited participants were divided into the NC group and the MCI group.

Ethics Statement

Written informed consent, witnessed oral consent, or kin written consent was obtained from all study participants or their family members. This study complied with the guidelines of the National Institutes of Health on the conduct of human research and was approved by the Ethical Committee of The First Affiliated Hospital of Chongqing Medical University on human research.

Data Collection

The survey of CGA sheet was performed by professional geriatricians via face-to-face interview in hospital or community service center, and CDR was further used after cognitive screening if necessary. Blood pressure (BP) was measured under resting condition. Heart condition was assessed by electrocardiogram and color doppler ultrasound. Cerebrovascular disease was evaluated by neurological examination and computed tomography/magnetic resonance imaging scan of brain. Blood samples were analyzed, including blood routine, liver function, kidney function, triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).

The diagnosis of hypertension fulfilled the criteria of the 2011 guide of American College of Cardiology and the American Heart Association (ACCF/AHA), and hypertension was diagnosed with the systolic BP (SBP) $\geq$140 mm Hg and/or the diastolic BP (DBP) $\geq$90 mm Hg. The diagnosis of CHD fulfilled the criteria of the 2011 guide of ACCF/AHA, and CHD was defined as a history of silent myocardial ischemia, angina pectoris, myocardial infarction, or ischemic cardiomyopathy. Cerebrovascular disease was identified as a history of transient ischemic attack (TIA) or stroke.

The diagnosis criteria of MCI included subjective complaint of memory decline for at least 6 months; objective memory decline via neuropsychological evaluation, CDR score of 0.5; decline in performing the normal activities of daily living; inconformity to dementia diagnostic criteria; and no history of alcoholism and drug abuse. When the participants had scored 0 for all CDR items, they were categorized as the NC group.

Statistical Analysis

Distributions of continuous data were represented by the mean and standard deviation (SD; mean $\pm$ SD). Normality of all continuous data was tested by Kolmogorov-Smirnov test. Independent t test (normally distributed) and Mann-Whitney U test (nonnormally distributed) were used for continuous data. Distribution of categorical data was represented by ratio (%). The χ^2 test was used for comparison of categorical data. To show the correlation between VRFs and cognitive function in our study, logistic regression analysis was used to analyze VRFs impacting MCI. The analysis of all data was carried out with SAS statistics 9.1. A P value of less than .05 was considered to be significant.

Results

A total of 603 participants were included in this study; however, 6 participants did not complete CGA due to practice reason. Therefore, 597 participants were enrolled in the cross-sectional study.

The age of our cohort ranged from 60 to 95 years; 219 (36.7%) participants of 60 to 69 years, 237 (39.7%) participants of 70 to 79 years, and 141 (23.6%) participants of $\geq$80 years. In all, 55.95% (334 of 597) of patients had hypertension for the duration of 13.88 $\pm$ 11.16 years; 28.81% (172 of 597) of patients had CHD, for the duration of 10.45 $\pm$ 8.88 years; and 17.09% (102 of 597) of patients had CVD, for the duration of 5.20 $\pm$ 6.28 years.

A total of 457 (76.5%) patients belonged to the NC group and 140 (23.5%) patients to the MCI group. Mini-Mental State Examination score of the MCI group was significantly lower than that of the NC group (21.03 $\pm$ 4.50 vs 28.80 $\pm$ 1.30, respectivel, $P < .05$). Demographic and clinical characteristics

Table 1. Demographic Characteristics of Participants With NC and MCI.

Basic Condition	NC (n = 457)	MCI (n = 140)	*P* Value
Age, mean ± SD	71.44 ± 7.78	77.92 ± 6.78	.000[a]
Gender, n (%)			.058
Male	208 (45.51%)	51 (36.43%)	
Female	249 (54.49%)	89 (63.57%)	
Education, n (%)			.027[a]
≤12 years	333 (72.87%)	115 (82.14%)	
>12 years	124 (27.13%)	25 (17.86%)	
MMSE score	28.80 ± 1.30	21.03 ± 4.50	.000[a]

Abbreviations: NC, normal cognition; MCI, mild cognitive impairment; SD, standard deviation; MMSE, Mini-Mental State Examination.
[a] $P < .05$ represents statistical significance.

Table 2. Clinical Characteristics of Participants With NC and MCI.

Basic Condition	NC (n = 457)	MCI (n = 140)	*P* Value
Diseases, n (%.)			
Hypertension	241 (52.74%)	93 (66.43%)	.000[a]
CHD	121 (26.48%)	51 (36.43%)	.023[a]
CVD	72 (15.75%)	30 (21.43%)	.119
Blood pressure, mm Hg			
SBP	131.74 ± 16.78	137.63 ± 18.90	.000[a]
DBP	77.37 ± 10.12	77.00 ± 10.81	.658
Blood lipid, mmol/L			
TG	1.60 ± 1.01	1.55 ± 1.86	.117
TC	4.96 ± 2.18	4.59 ± 1.21	.015[a]
HDL-C	1.39 ± 0.41	1.36 ± 0.45	.316
LDL-C	2.86 ± 0.93	2.67 ± 0.90	.048[a]

Abbreviations: NC: normal cognition; MCI: mild cognitive impairment; CHD, coronary heart disease; CVD, cerebrovascular disease; SBP, systolic pressure; DBP, diastolic pressure; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
[a] $P < .05$ represents statistical significance.

of patients with NC and MCI were listed in Tables 1 and 2, respectively. After adjusting for age, gender, and education, logistic regression analysis demonstrated that hypertension, CHD, SBP, TC, and LDL-C were independently associated with MCI ($P < .05$; Table 3). However, CVD, DBP, TG, and HDL-C were not independently associated with MCI ($P > .05$).

There were 211 (35.34%) individuals without vascular disease, 205 (34.34%) with 1 vascular disease, 141 (23.62%) with 2 vascular diseases, and 40 (6.70%) with 3 vascular diseases. The incidence of MCI was 14.69% (31 of 211) in the subgroup with no vascular disease, 27.80% (57 of 205) with 1, 28.37% (40 of 141) with 2, and 30.00% (12 of 40) with 3 diseases, respectively. Vascular disease was closely associated with MCI in this study. Patients with vascular diseases had higher risks of MCI than those without vascular disease ($P < .05$); however, patients with 2 or more vascular diseases did not show higher risk of MCI than patients with 1 vascular disease ($P > .05$; Table 4).

Table 3. Association of Vascular Risk Factors With MCI Adjusted for Age, Gender, and Education.

Basic Condition	OR (95% CI)	*P* Value
Diseases		
Hypertension	0.979 (0.971-0.987)	.000[a]
CHD	0.988 (0.981-0.996)	.001[a]
Blood pressure, mm Hg		
SBP	0.958 (0.951-0.964)	.000[a]
Blood lipid, mmol/L		
TC	0.944 (0.931-0.957)	.000[a]
LDL-C	0.940 (0.929-0.952)	.000[a]

Abbreviations: MCI, mild cognitive impairment; CHD, coronary heart disease; SBP, systolic pressure; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; OR (95% CI), odds ratio (95% confidence intervals).
[a] $P < .05$ represents statistical significance.

Table 4. Association of Vascular Diseases With Cognitive Function Adjusted for Age and Education.[a]

Varieties	NC (n = 457)	MCI (n = 140)	*P* Value
A: No disease	180	31	
B: 1 disease (hypertension, CHD, CVD)[a]	148	57	.001[b]
C: 2 diseases (hypertension + CHD, hypertension + CVD, CHD + CVD)[a]	101	40	.002[b]
D: 3 diseases (hypertension + CHD + CVD)[a]	28	12	.018[b]

Abbreviations: NC: normal cognition; MCI: mild cognitive impairment; CHD, coronary heart disease; CVD, cerebrovascular disease.
[a] Represented $P > .05$ (any 2 groups from B, C, or D), $P > .05$ was considered as no significance.
[b] Represented $P < .05$ (B, C, D vs A), $P < .05$ was considered as significance.

Discussion

The present study has shown that several VRFs are associated with MCI in Chinese elderly people of Chongqing region. Hypertension and CHD are independent VRFs for MCI. Mild cognitive impairment is more likely to present in patients with vascular diseases than those without vascular diseases. Moreover, abnormal SBP, TC, and LDL-C also significantly contribute to MCI. Approximately 130 mm Hg of SBP level should be controlled to prevent MCI; 4.96 mmol/L of TC level and 2.66 mmol/L of LDL-C level are suitable for the prevention of MCI. Higher SBP, lower TC, and LDL-C can contribute to MCI in the elderly population. However, there was no significant difference in CVD, DBP, TG, HDL-C, and increased types of vascular diseases.

Hypertension is not only associated with cognitive impairment but also increases the risk of dementia.[13] However, the association between hypertension and cognitive impairment may be related to BP levels. Higher BP levels or elevated pulse pressure significantly increases the risk of cognitive impairment,[14-16] while other studies show even lower BP levels with higher risk of cognitive impairment.[17-19] Therefore, both high BP and low BP affect brain perfusion and cognitive function

because of multiple pathophysiological pathways, including cerebral hypoperfusion-induced hypoxia/ischemia, increased β-amyloid accumulation in brain vessels, and vascular damage mediated by atherosclerosis and oxidative stress.[20-24] It is also suggested that in patients who developed dementia, SBP showed a greater increase from midlife to late life and a greater decrease in late life, but DBP showed no significant changes.[25] Consistent with the most findings, our present study demonstrated that hypertension was associated with MCI and higher SBP levels contributed to the risk of MCI in the elderly population, and there was no association between DBP and MCI. Increasing evidence has suggested that antihypertensive agents have a decreased risk of dementia in individuals with hypertension; and antihypertensive treatments need to be carried out in early stage; however, BP control levels preventing the development of dementia are not inconclusive. According to our results, SBP levels should be controlled at approximately 130 mm Hg to prevent MCI.

Recently, several studies find that CHD is associated with cognitive decline, such as executive function, global cognition, and nonamnestic MCI, and promotes the risk of vascular cognitive impairment and VD.[26-29] However, other studies have found no significant contribution of CHD to cognitive impairment.[30-32] Therefore, the relation between CHD and MCI is still contradictory. The present study support that CHD is associated with MCI. The relationship between cognitive impairment and CHD can be explained by reduced cardiac pump function,[33] because lower scores for cognitive function are detected in patients with lower ejection fraction or reduced cardiac output.[34] Therefore, CHD-causing impaired cardiac function may give rise to cerebral hypoperfusion, subsequently lead to hypometabolism, cerebrovascular pathology, and brain atrophy, and eventually contributes to cognitive impairment.[35-37]

Cerebrovascular disease, especially stroke, increases the risk of both MCI and AD[32,38] via increase in β-amyloid production/accumulation and inflammation-associated hippocampal atrophy.[39,40] Cerebrovascular disease consists of multiple subtypes; variant CVD subtype shows different risk for MCI. For instance, a study shows that the annual prevalence of cognitive impairment is higher in small vessel occlusion than that in lacunar infarction (10% vs 2%), up to 5 years after stroke.[41] Another study finds no relationship between TIA and MCI; and stroke significantly increases the risk of MCI after adjustment for demographics.[32] However, onset time of TIA probably contributes to cognitive impairment. It is reported that patients with prestroke TIA <4 weeks had a higher risk of dementia than those with a prestroke TIA ≥4 weeks and without TIA. Moreover, the association between TIA and dementia depends on age, and there is no significance between TIA and dementia in patients aged more than 75 years.[42] In addition, the risk of cognitive impairment is also associated with low baseline cognition before CVD.[43] Our results show no significant correlation between CVD and MCI. This phenomenon is possibly explained by age. In all, 141 (23.6%) patients (≥80 years old) are enrolled in this study, which may affect our results. In addition, there are only 102 (17.09%) patients with CVD in this study and the limited sample size probably results statistic bias. Therefore, we need to enlarge the sample size of the study and follow-up this cohort in further work.

Our results also show that patients with vascular diseases have a higher risk of MCI than those without vascular diseases. However, combinations of vascular diseases including hypertension, CHD, and CVD do not reach a higher risk of MCI in this study. In other words, patients with 1 vascular disease had the same MCI risk as those with 2 or 3 vascular diseases. Although CVD is not independently associated with MCI in this study, this result suggests that the relationship between CVD and MCI is influenced by hypertension and CHD and demonstrates that hypertension and CHD are important risk factors for CVD-associated cognition.

Dyslipidemia is a known risk factor for cognitive impairment, especially for AD. Both hypercholesterolemia and hypertriglyceridemia lead to cognitive impairment via β-amyloid generation, τ hyperphosphorylation, and inflammation in the brain.[44,45] However, to our knowledge, it is controversial for the association between dyslipidemia and cognitive impairment. Some studies demonstrate that dyslipidemia such as higher TG, TC, LDL-C, and lower HDL-C contributes to the progression of AD,[46,47] while other studies find no associations between dyslipidemia and cognitive impairment.[48] Even the relationship between blood lipid and cognitive impairment may vary considerably depending on age. High TC levels in late life (>70 years old) reduce the risk of cognitive impairment.[49] Higher TC and LDL-C levels are associated with better memory function in very elderly population.[50] The present study demonstrates that lower TC and lower LDL-C are associated with MCI adjusting for age, sex, and education; but TG and HDL-C were not associated with MCI. In our cohort, 63.3% of participants reached 70 years or more, thus, adequate levels of TC and LDL-C may be a protective factor for cognitive function in very elderly population. Meanwhile, this study may provide a useful reference on treatment of hyperlipidemia for clinicians. According to our results, 4.96 mmol/L of TC level and 2.66 mmol/L of LDL-C level are suitable for cognitive function, and lower TC and LDL-C lead to cognitive impairment in the elderly population. In addition, 1 study shows that high normal TG level is conducive to preservation of cognitive function in Chinese elderly people (>80 years).[51] However, TG has no important role in MCI in our population. Moreover, individuals with higher HDL-C levels have a significantly lower risk of dementia.[52] Lower HDL-C level is associated with more severe lesions of white matter changes, leading to amnestic MCI.[53] However, our report does not show HDL-C has a correlation to MCI.

We have to acknowledge a few limitations in this study. First, this is only a cross-sectional study with a relatively small number of samples, and there are no follow-up data. There is lacking of brain imaging or biomarker data (such as apolipoprotein E 4 allele), thus the risk from MCI to dementia cannot be predicted in this study. Therefore, a follow-up study, brain imaging, and biomarker tests will be performed in the future.

In summary, hypertension, CHD, SBP, TC, and LDL-C are independent risk factors of MCI. Moreover, patients with vascular diseases have a higher risk of MCI, but combinations of vascular diseases do not increase the risk of MCI. We suggest that 130 mm Hg of SBP, 4.96 mmol/L of TC, and 2.66 mmol/L of LDL-C may be suitable for elder people to prevent the progression of cognitive impairment.

Authors' Note

The authors Yan Zou and Qinlan Zhu equally contributed to this article.

Declaration of Conflicting Interests

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References

1. Manly JJ, Tang M, Schupf N, Stern Y, Vonsattel JP, Mayeux R. Frequency and course of mild cognitive impairment in a multiethnic community. *Ann Neurol*. 2008;63(4):494-506.
2. Plassman BL, Langa KM, Fisher GG, et al. Prevalence of cognitive impairment without dementia in the United States. *Ann Intern Med*. 2008;148(6):427-434.
3. Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Alzheimer's disease. *Lancet*. 2011;377(9770):1019-1031.
4. Austin BP, Nair VA, Meier TB, et al. Effects of hypoperfusion in Alzheimer's disease. *J Alzheimers Dis*. 2011;26(suppl 3): 123-133.
5. Okamoto Y, Yamamoto T, Kalaria RN, et al. Cerebral hypoperfusion accelerates cerebral amyloid angiopathy and promotes cortical microinfarcts. *Acta Neuropathol*. 2012;123(3):381-394.
6. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/American stroke association. *Stroke*. 2011;42(9):2672-2713.
7. Power MC, Weuve J, Gagne JJ, McQueen MB, Viswanathan A, Blacker D. The association between blood pressure and incident Alzheimer disease: a systematic review and meta-analysis. *Epidemiology*. 2011;22(5):646-659.
8. Roberts RO, Knopman DS, Geda YE, Cha RH, Roger VL, Petersen RC. Coronary heart disease is associated with non-amnestic mild cognitive impairment. *Neurobiol Aging*. 2010;31(11):1894-1902.
9. Pimentel-Coelho PM, Rivest S. The early contribution of cerebrovascular factors to the pathogenesis of Alzheimer's disease. *Eur J Neurosci*. 2012;35(12):1917-1937.
10. Deschaintre Y, Richard F, Leys D, Pasquier F. Treatment of vascular risk factors is associated with slower decline in Alzheimer disease. *Neurology*. 2009;73(9):674-680.
11. Fromm A, Lundervold AJ, Moen G, Skulstad S, Thomassen L. A vascular approach to mild amnestic cognitive impairment: a pliot study. *Acta Neurol Scand*. 2013;127(suppl 196):73-76.
12. Devine ME, Fonseca JA, Walker Z. Do cerebral white matter lesions influence the rate of progression from mild cognitive impairment to dementia? *Int Psychogeriatr*. 2013;25(1):120-127.
13. Wysocki M, Luo X, Schmeidler J, et al. Hypertension is associated with cognitive decline in elderly people at high risk for dementia. *Am J Geriatr Psychiatry*. 2012;20(2):179-187.
14. Yasar S, Ko JY, Nothelle S, Mielke MM, Carlson MC. Evaluation of the effect of systolic blood pressure and pulse pressure on cognitive function: the Women's Health and Aging Study II. *PLoS One*. 2011;6(12):e27976.
15. Tsivgoulis G, Alexandrov AV, Wadley VG, et al. Association of higher diastolic blood pressure levels with cognitive impairment. *Neurology*. 2009;73(8):589-595.
16. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol*. 2005;4(8):487-499.
17. Sierra C, Doménech M, Camafort M, Coca A. Hypertension and mild cognitive impairment. *Curr Hypertens Rep*. 2012;14(6): 548-555.
18. Hebert LE, Scherr PA, Bennett DA, et al. Blood pressure and late-life cognitive function change: a biracial longitudinal population study. *Neurology*. 2004;62(11):2021-2024.
19. Li G, Rhew IC, Shofer JB, et al. Age-varying association between blood pressure and risk of dementia in those aged 65 and older: a community-based prospective cohort study. *J Am Geriatr Soc*. 2007;55(8):1161-1167.
20. Novak V, Hajjar I. The relationship between blood pressure and cognitive function. *Nat Rev Cardiol*. 2010;7(12):686-698.
21. Kerola T, Kettunen R, Nieminen T. The complex interplay of cardiovascular system and cognition: how to predict dementia in the elderly? *Int J Cardiol*. 2011;150(2):123-129.
22. Carnevale D, Mascio G, D'Andrea I, et al. Hypertension induces brain β-amyloid accumulation, cognitive impairment, and memory deterioration through activation of receptor for advanced glycation end products in brain vasculature. *Hypertension*. 2012;60(1):188-197.
23. Grassi D, Ferri L, Cheli P, Di Giosia P, Ferri C. Cognitive decline as a consequence of essential hypertension. *Curr Pharm Des*. 2011;17(28):3032-3038.
24. Sharp SI, Aarsland D, Day S, Sønnesyn H, Alzheimer's Society Vascular Dementia Systematic Review Group, Ballard C. Hypertension is a potential risk factor for vascular dementia: systematic review. *Int J Geriatr Psychiatry*. 2011;26(7):661-669.
25. Stewart R, Xue QL, Masaki K, et al. Change in blood pressure and incident dementia: a 32-year prospective study. *Hypertension*. 2009;54(2):233-240.
26. Zheng L, Mack WJ, Chui HC, et al. Coronary artery disease is associated with cognitive decline independent of changes on magnetic resonance imaging in cognitively normal elderly adults. *J Am Geriatr Soc*. 2012;60(3):499-504.

27. Bajenaru O, Antochi F, Tiu C. Particular aspects in patients with coronary heart disease and vascular cognitive impairment. *J Neurol Sci*. 2010;299(1-2):49-50.
28. Selnes OA, Grega MA, Bailey MM, et al. Do management strategies for coronary artery disease influence 6-year cognitive outcomes? *Ann Thorac Surg*. 2009;88(2):445-454.
29. Singh-Manoux A, Sabia S, Lajnef M, et al. History of coronary heart disease and cognitive performance in midlife: the Whitehall II study. *Eur Heart J*. 2008;29(17):2100-2107.
30. Bursi F, Rocca WA, Killian JM, et al. Heart disease and dementia: a population-based study. *Am J Epidemiol*. 2006;163(2):135-141.
31. Arntzen KA, Schirmer H, Wilsgaard T, Mathiesen EB. Impact of cardiovascular risk factors on cognitive function: the Tromsø study. *Eur J Neurol*. 2011;18(5):737-743.
32. Ganguli M, Fu B, Snitz BE, Hughes TF, Chang CC. Mild cognitive impairment: incidence and vascular risk factors in a population-based cohort. *Neurology*. 2013;80(23):2112-2120.
33. Eggermont LH, de Boer K, Muller M, Jaschke AC, Kamp O, Scherder EJ. Cardiac disease and cognitive impairment: a systematic review. *Heart*. 2012;98(18):1334-1340.
34. Jefferson AL, Himali JJ, Au R, et al. Relation of left ventricular rejection fraction to cognitive aging (from the Framingham Heart Study). *Am J Cardiol*. 2011;108(9):1346-1351.
35. Jefferson AL, Himali JJ, Beiser AS, et al. Cardiac index is associated with brain aging: the Framingham Heart Study. *Circulation*. 2010;122(7):690-697.
36. Appelman AP, van der Graaf Y, Vincke n KL, Mali WP, Geerlings MI. Combined effect of cerebral hypoperfusion and white matter lesions on executive functioning—The SMART-MR stud y. *Dement Geriatr Cogn Disord*. 2010;29(3):240-247.
37. Mazza M, Marano G, Traversi G, Bria P, Mazza S. Primary cerebral blood flow deficiency and Alzheimer's disease: shadows and lights. *J Alzheimers Dis*. 2011;23(3):375-389.
38. Pinkston JB, Alekseeva N, Gonzalez Toledo E. Stroke and dementia. *Neurol Res*. 2009;31(8):824-831.
39. Honjo K, Black SE, Verhoeff NP. Alzheimer's disease, cerebrovascular disease, and the β-amyloid cascade. *Can J Neurol Sci*. 2012;39(6):712-728.
40. Kliper E, Ben Bashat D, Bornstein NM, et al. Cognitive decline after stroke: relation to inflammatory biomarkers and hippocampal volume. *Stroke*. 2013;44(5):1433-1435.
41. Douiri A, Rudd AG, Wolfe CD. Prevalence of poststroke cognitive impairment South London stroke register 1995–2010. *Stroke*. 2013;44(1):138-145.
42. Jacquin A, Aboa-Eboulé C, Rouaud O, et al. Prior transient ischemic attack and dementia after subsequent ischemic stroke. *Alzheimer Dis Assoc Disord*. 2012;26(4):307-313.
43. Rist PM, Chalmers J, Arima H, et al. Baseline cognitive function, recurrent stroke, and risk of dementia in patients with stroke. *Stroke*. 2013;44(7):1790-1795.
44. Park SH, Kim JH, Choi KH, et al. Hypercholesterolemia accelerates amyloid β-induced cognitive deficits. *Int J Mol Med*. 2013;31(3):577-582.
45. Frisardi V, Solfrizzi V, Seripa D, et al. Metabolic-cognitive syndrome: a cross-talk between metabolic syndrome and Alzheimer's disease. *Ageing Res Rev*. 2010;9(4):399-417.
46. Matsuzaki T, Sasaki K, Hata J, et al. Association of Alzheimer disease pathology with abnormal lipid metabolism: the Hisayama Study. *Neurology*. 2011;77(11):1068-1075.
47. Altman R, Rutledge JC. The vascular contribution to Alzheimer's disease. *Clin Sci (Lond)*. 2010;119(10):407-421.
48. Koyama A, Stone K, Yaffe K. Serum oxidized low-density lipoprotein level and risk of cognitive impairment in older women. *Neurobiol Aging*. 2013;34(2):634.e2-635.e2.
49. Mielke MM, Zandi PP, Sjögren M, et al. High total cholesterol levels in late life associated with a reduced risk of dementia. *Neurology*. 2005;64(10):1689-1695.
50. West R, Beeri MS, Schmeidler J, et al. Better memory functioning associated with higher total and low-density lipoprotein cholesterol levels in very elderly subjects without the apolipoprotein e4 allele. *Am J Geriatr Psychiatry*. 2008;16(9):781-785.
51. Yin ZX, Shi XM, Kraus VB, et al. High normal plasma triglycerides are associated with preserved cognitive function in Chinese oldest-old. *Age Ageing*. 2012;41(5):600-606.
52. Anstey KJ, Lipnicki DM, Low LF. Cholesterol as a risk factor for dementia and cognitive decline: a systematic review of prospective studies with meta-analysis. *Am J Geriatr Psychiatry*. 2008;16(5):343-354.
53. Zhuang L, Sachdev PS, Trollor JN, et al. Microstructural white matter changes, not hippocampal atrophy, detect early amnestic mild cognitive impairment. *PLoS One*. 2013;8(3):e58887.