Later Onset of Hypertension Increased the Risk of Dementia in Mild Cognitive Impairment

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Abstract

Objective To investigate the effect of hypertension development on the progression of MCI for middle aged and elderly people. Methods A population-based longitudinal cognition survey of people aged 55+ was conducted. The hypertension onset age was estimated by self-reported information and medical insurance card records. In order to study the effect of later onset of hypertension on dementia, the incidence of dementia was compared between the two groups. Results A total of 277 h ypertensive mild cognitive impairment (MCI) participants without dementia were followed for 6 years. Overall, 56 MCI participants (20.22%) progressed to dementia (MCIp). The proportion of MCIp participants in the old-age onset hypertension group (≥ 65 years) was higher than that of middle-age onset one (27.0% vs 15.4%; X 2 = 5.538, P = 0.019). And in the old-age onset hypertension group, the proportion of MCIp without diabetes mellitus was higher than those with diabetes mellitus (24.7% vs 12.6%; X 2 = 5.321, P = 0.021), and the proportion of MCIp with increased pulse pressure was higher than those without increased pulse pressure (33.3% vs 15.4%; X 2 = 3.902, P = 0.048). However, the multivariate logistic regression analysis showed that older age was the only risk for MCIp (OR=0.732, p=0.029). Conclusions These results suggest that, later onset hypertension was harmful to cognition even in cases where the level of blood pressure maintained at 130/80 mmHg with antihypertensive management.

Background

With the advent of population aging, the population of dementia continues to rise, with approximately 47 million people in the whole world in 2015, which is expected to triple by 2050[1]. The two most common types of dementia are Alzheimer's disease (AD) and Vascular dementia (VaD), accounting for about 80% [1-3]. Mild Cognitive Impairment (MCI) is an intermediate transition stage between normal aging and dementia, which is characterized by mild impairment of cognitive function without decline of daily living or social functioning, and previous studies has shown that all MCI eventually progressed to dementia (MCI progression, MCIp) after 9 years[4]. A multicenter research performed in China from 2008 to 2009 showed that the prevalence rates of MCI and dementia (> 65 years old) were as high as 20.8% and 5.14% respectively [5].

Hypertension is another disease that compromises with the abilities of daily living of the elderly [6, 7]. In the recent twenty years, several studies have found that hypertension is a risk factor not only for Alzheimer's disease, but also for MCI [2, 7-10]. In a 2 years follow-up study of 385 MCI cases, Goldstein FC et al. showed that, compared to subjects without hypertension, the cognitive function (such as attention, executive function and naming) of subjects with hypertension declined significantly, especially those with Systolic blood pressure (SBP) ≥ 140 mmHg or Diastolic Blood Pressure (DBP) ≥ 90 mmHg[11]. In other words, hypertension is a risk factor for MCI progression. To date, there is no confirmative effect of nootropic drugs on dementia, whereas hypertension is a very important controllable vascular risk factor[2]. Therefore, it is crucial to quickly identify and manage high-risk patients with hypertension, which will prevent dementia effectively.

It has been found that the incidence of dementia is related to the age onset of hypertension. Numerous studies have shown that middle-aged hypertension is associated with increased dementia twenty or thirty years later, but it is uncertain of later onset hypertension (≥65 years) [9, 12]. For example, some studies have found that hypertension is independently associated with cognitive impairment in later life, the cognitive function declining with increasing SBP, especially SBP ≥ 180mmHg [13-15]. In Yuan’s study, the cognition declined with the increased SBP like a hockey [16]. It was also confirmed by cross-sectional survey that, in dementia group, not only the proportion of hypertension (76.5% vs 59.3%), but also the SBP level was higher than that of MCI group [15]. However, some previous studies performed ten years ago showed that hypertension does not necessarily increase the risk of dementia [2, 17-22]. A 10-year follow-up (averaging 2.8 years) study of 559 over 90 year-olds conducted by Corrada MM et al. had found that the risk of dementia in hypertensive patients aged 80 and 90 was lower than that in non-hypertensive patients [17]. Nevertheless, high SBP

level was possibly associated with increased risk of dementia for <75 year-olds, and it was not the case for >80 year-olds [19-22]. Moreover, not the high SBP level, but the increased pulse pressure (PP) was negatively correlated with cognition [23].

Our previous epidemiological investigation found that MCI with newly onset hypertension (≥ 60 years old) had a higher rate of dementia. We then put forth the hypothesis that there may be a particular age (between 55 and 75 years old) when hypertension is particularly harmful to cognitive function. Our objective was to evaluate the association between later onset of hypertension and the risk of all-cause dementia in a population-based cohort of individuals.

Materials And Methods

1.1 Subjects

The current research was carried out in Pudong district in Shanghai. We analyzed the elderly with MCI (age ≥ 55 years old) who had participated in a survey from June 2011 to June 2012 (No. PKJ2010-Y26) and were successfully contacted in the later survey in 2017. All participants have signed informed consent. Only those sufficiently educated, with enough audiovisual level to complete the necessary examinations were included.

According to the age onset of hypertension, the participants were divided into the old-aged group (onset age ≥ 65 years) and the middle-aged group (onset age <65 years).

1.2 MCI and dementia diagnostic criteria

MCI was diagnosed using the Petersen's diagnostic criteria: (1) the elderly consciously exhibited memory loss, especially those with memory impairment for more than 3 months; (2) the overall cognitive function is normal through the Mini-mental state examination (MMSE total score: illiterate subjects > 17, with primary school education > 20 points, and others > 24 point); (3) clinical dementia rating (CDR) score reached a level of 0.5; (4) Montreal cognitive assessment scale: MoCA score ≤ 26; (5) with normal function of daily life; (6) the patient did not meet the diagnostic criteria for dementia [24, 25].

The criteria for dementia were as follow. (1) MMSE test: illiterate subjects ≤ 17, subjects with primary school education ≤ 20 points, subjects with education of middle school or above ≤ 24 points [26]; (2) Those subjects above without definite blindness or speech difficulties.

1.3 Cognitive and other neuropsychological assessments

Subjects received the cognitive and other neuropsychological assessments using the following scales where possible: (1) the mini-mental state examination (MMSE) scale [26], (2) Montreal cognitive assessment (MoCA) [25], (3) Hamilton Depression Scale (HAMD-17) [27] , (4) Hachinski ischemic index scale (HIS) [28], (5) Activity of Daily Life Scale (ADL) [29], (6) the clinical dementia rating (CDR) scale [30].

1.4 Diagnosis and treatment of hypertension

The diagnosis, duration, age of onset, stage and treatment of hypertension were according to elderly self-report and examination of their medical insurance card records.

1.5 Additional variables:

Other medical histories reported at the baseline visit and considered as potential confounders included stroke, transient ischemic attack, diabetes, heart disease, and depression. Heart disease included any of the following diseases or

surgeries: coronary artery disease, myocardial infarction, atrial fibrillation or other arrhythmias, heart valve disease, congestive heart failure, coronary artery bypass, or pacemaker placement. The highest level of education attained, marital status and occupation were also recorded.

1.6 Statistical approach:

Data were analyzed using the Statistical Package for Social Sciences (version 19.0; SPSS, IBM, Chicago, IL, USA). Continuous variables were tested for normality by One-Sample Kolmogorov-Smirnov Test. Continuous variables were expressed as mean±SD or median (range) as per distribution type, and categorical data were expressed as frequency and percentages. Statistical analysis was performed using independent samples t-test for normal data and Mann-Whitney U test for non-normal data. Categorical data was analyzed by Chi-square test. The multivariate logistic regression analysis was conducted to identify the determinants of outcome of MCI following-up. A P value of less than 0.05 was considered statistically significant.

Results

2.1 Follow-up outcomes of hypertensive MCI in community

There were 56 individuals (20.22%) who progressed to dementia (MCIp) while 221 (79.78) remained stable (MCIs). In comparison with MCIs, MCIp individuals demonstrated significantly worse performance in CDR and ADL scores ($p < 0.01$). Besides, MCIp individuals were more likely to be single ($p = 0.022$) (Table 2), which could be both the reason and consequence of cognitive function deterioration. Next, all individuals were divided into two groups according to the onset time of hypertension: the proportion of MCIp participants in the old-age onset hypertension group (≥ 65 years) was significantly higher than that of middle-age onset one (27.0% vs 15.4%; $X2 = 5.538$, $p = 0.019$). However, this may be due to that the old-age onset group had a higher age compared with the middle-age onset group (77.75±6.75 vs70.45±6.41, $p<0.001$). In the old-age onset hypertension group, the proportion of MCIp without diabetes mellitus was higher than those with diabetes mellitus (24.7% vs 12.6%; $X2 = 5.321$, $P = 0.021$), and the frequency of MCIp with increased pulse pressure was higher than those without increased pulse pressure (33.3% vs 15.4%; $X2 = 3.902$, $P = 0.048$). This result implied that for individuals with a later onset of hypertension, increased pulse pressure does link to CI progression.

2.2 Multivariate Logistic Regression Analysis of Cognitive Function deterioration in MCI

The multivariate logistic regression model was fitted to analyze the determinants of the outcome of MCI following-up (MCIp = 1, MCIs = 0). Demographic data and variables such as hypertension, age at onset of hypertension, blood pressure grouping, and pulse pressure were taken as independent variables into the model. The variables assignment of logistic regression analysis was listed in table 3. The results showed that age ($P=0.029$, $OR = 0.732$) was the only independent determinant of outcome of MCI following-up, that the patients with a younger age are the more likely to control the cognitive function (Table 4). Other factors demonstrated no significant association with MCIp ($P>0.05$).

Discussion

Main Findings

3.1 The MCIp was higher in the group of onset ≥ 65 years.

In this prospective study of 277 mild cognitive impairment participants aged 73.48±7.47, later onset of hypertension group (≥65 years) was related to a higher dementia risk compared with middle-age. This increased risk was limited to participants who reported mean SBP was 130/80 mmHg. In addition, the differences disappeared after stratification

according to age, BMI, SBP and DBP levels. To our knowledge, our study is the first to report the level of blood pressure and to include hypertension by age of onset.

Some researchers found that the increased risk of dementia was related to the increase of SBP in the group under 75 years old [17]. The risk of cognitive impairment increased by 1.17 times when SBP was 130-139 mmHg, however, it increased to 1.54 times when SBP was≥180 mmHg [16]. The results of 3.8-year follow-up of hypertension (n=2800) showed that incidences of MCI and dementia could decrease by 15% in intensive control of blood pressure (SBP<120 mmHg) compared with the standard control group (SB<140 mmHg) (HR = 0.85, 95% CI = 0.74-0.97, P = 0.02) [31]; moreover, statistically significant reduced risk of MCI and dementia can be found in the intensive group (SBP =120 mmHg) less than 75 years old[32].

The results of this study are not consistent with some results previously published. The reasons may be as follows: Firstly, the average age of the participants in this study was 73 years old with mean SBP 130/80 mmHg, 57% of them were less than 75 years old, 8 cases (2.89%) with SBP < 120 mmHg and 8 (2.89%) with SBP ≥160 mmHg. Our sample size was relatively small. Secondly, through medication management with a goal of normal range (130/80 mmHg), the proportion of MCIp was different between the two groups, suggesting that aggressive lowering of systolic blood pressure may not good for the elderly [2]. Similar findings were found in long-term large sample study (n=1440, 8 years follow-up), the risk of dementia increased by 2.4 times when blood pressure was less than 140/90 mmHg with hypertension from middle to old age.

Furthermore, some studies have found that the relationship between the risk of dementia and the increase of SBP was not clear yet for those older than 85 years [17]. After 10 years of follow-up (average 2.8 years, n=559), Corrada MM et al. reported that the risk of dementia in newly onset hypertension aged 80+ and 90+ was lower than that in non-hypertensive patients (HR 0.54 and 0.37, P 0.04 and 0.004, respectively) [17]. The results suggested that the mechanism of hypertension in the elderly was different from that in the middle-aged cohort. Hypertension may be a result of compensatory or response of the body. That is to say, the etiology of hypertension is similar to that of dementia, but the clinical symptoms occur at different times.

In addition, the cognitive impacts of middle-aged hypertension can only be followed up and analyzed after excluding cerebrovascular accidents [21], that is to say, there is bias in the samples. The patients with middle-aged onset hypertension are too serious to detect the impact of hypertension on AD because of cerebrovascular damage such as stroke [22]. In addition, other community studies have found that middle-aged hypertension is associated with MCI and dementia at the age of 70-90 (more strongly associated with dementia) [23]. Namely, this part of the population did not go through the MCI stage and directly entered the dementia stage, which is also an aspect of sample bias.

3.2 The MCIp frequency was higher in the group without diabetes mellitus.

Another finding of our study was that for hypertensive MCI without diabetes mellitus, the rate of MCIp in the old-age group was 1.96 times higher than that in the middle-age one. One Meta-analysis also found that the predictive ability of cerebrovascular risk factors for dementia/AD in the old-age group (average age 72.3-82.5) was significantly reduced [33]. That is, cerebrovascular diseases such as hypertension, diabetes, hyperlipidemia did not necessarily increase the risk of dementia. A large sample survey of community-based brain magnetic resonance imaging (MRI) follow-up (n = 2367) revealed that cerebrovascular risk factors such as white matter degeneration, hypertension, diabetes, smoking were associated with aging and contributed more to dementia, although the age range of this survey was 20-90 years[19]. It should be considered that only 61 cases (22.02%) of diabetes mellitus in this study may be due to insufficient sample size, which makes it difficult to reflect statistical differences. In addition, for MCI aged 73.48 (SD=7.47), the pathogenesis of diabetes mellitus may be different from that of middle age, so the effect of diabetes mellitus on dementia is also different.

3.3 The MCIp was higher in the group with increased pulse pressure

The results of this study showed that, the MCIp was higher in the increased pulse pressure group, as compared to the normal pulse pressure group. Pulse pressure is a sign of arterial stiffness. It was found that pulse pressure was not associated with hypertension and apolipoprotein E4 but with the deposition of beta-amyloid plaques in the brain [23]. In other words, pulse pressure is closely related to aging.

Jefferson et al. used pulse wave velocity (PWV, m/sec) to measure aortic stiffness and found that the decrease of regional cerebral blood flow was related to the increase of arterial stiffness despite the existence of cerebral blood flow reserve capacity [34]. Follow-up and cross-sectional clinical studies have confirmed that increased pulse pressure increases the risk of dementia (including vascular dementia and Alzheimer's disease), which indicates that medicine may lead to occult hypotension and cerebral hypoperfusion [35].

3.4 MCIp cannot benefit from antihypertensive therapy

As for the prevention of dementia by antihypertensive therapy, some studies suggest that the risk of dementia is increased by the potential hypotension in antihypertensive therapy due to the impaired vascular regulation mechanism in the elderly [36-38]. A 16-week follow-up study suggested that people over 75 years old with MCI stopped taking antihypertensive drugs did not develop cognitive function deterioration [38]. They did not clarify whether all MCI cases had late-onset hypertension and their follow-up time was too short. A multicenter study found that hypertension patients over 65 years of age had a temporary increase in blood pressure four months after reducing antihypertensive medicine, but recovered to 134 mmHg in nine months, while the control group (without reducing drugs) had an increased risk of emergency hospitalization [20]. Animal experiments also suggested that sartan therapy can improve cognition in aged rats [39, 40]. However, clinical studies, as well as meta-analyses, reported that although antihypertensive therapy can reduce systolic or DBP, it cannot reduce the incidence of dementia [12, 17, 23, 41]. Together, for prevention of dementia in elderly with hypertension, a lot of exploration still need to be conducted.

3.5 Age, a risk factor for MCIp

In this study, regression analysis failed to decree age onset of hypertension, blood pressure and increased pulse pressure as risk factors for MCI deterioration, but only older age was found a risk factor. This is consistent with the results of other studies confirming that old age is the main risk factor for dementia [42].

3.6 Conclusion

Later onset hypertension was harmful to cognition even in cases where the level of blood pressure maintained at 130/80 mmHg with antihypertensive management. Those with hypertension occurring ≥ 65 years old may have a different pathogenesis from middle-aged hypertension.

Research limitations

First, 277 elderly people with hypertension in MCI community were followed up prospectively. The sample size was small, and the age distribution was uneven. The follow-up time was 6 years. There might be sample bias, and the proportion of MCIp was affected to some extent.

Secondly, the survey of occupational mental activity, post-retirement economic life, lifestyle, and other factors in MCI population with hypertension is not detailed enough, and the influence of insufficient sample size also has some influence on the results of the study.

Thirdly, the diagnosis of dementia in this study sample does not combine the detection of images and CSF biochemical indicators. The history and examination of hypertension are mainly provided by the community elderly and medical record card. There is no 24-hour ambulatory blood pressure monitoring, which may have some bias and have a certain impact on the objectivity of the results.

Research Significance

Firstly, the results of the current investigation show that MCI patients with hypertension ≥ 65 years old) with average age about 73 years old are prone to develop dementia, which suggests that comprehensive consideration should be given to antihypertensive drugs for hypertension (≥ 65 years old). Because of the different mechanisms of hypertension, maintaining blood pressure at 130/80 mmHg may not have a positive effect on the protection of cognitive function. Secondly, this study shows that pulse pressure has a negtive effect on the protection of cognitive function. In the group of increased pulse pressure, the proportion of senile patients progressing to dementia is higher than that of middle-aged patients. This suggests that, there may be different pathogenesis of hypertension in old age patients, and the effect of increased pulse pressure on cerebrovascular is also increased with age. Therefore, increased pulse pressure may be one of the risk factors of dementia. In the future, it is necessary to expand the research sample and improve the experimental methods for further confirmation.

Declarations

Ethics Approval and Consent to Participate

The research project was examined and approved by the ethics committee of the Mental Health Center of Pudong New Area, Shanghai 2017005).

Consent to publish

All the authors consent to publish.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing Interest

No Conflict of Interest.

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Authors Contribution

HY Qin and CP Hu guided the implementation of research, collated and analyzed the data. L Wang was responsible for the quality control and logistics support of the subject. Y Guo and ZC Cao were responsible for project implementation and data entry. XD Zhao and BG Zhu were the leaders and BG Zhu was the corresponding author.

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References

1. Livingston, G., et al., *Dementia prevention, intervention, and care.* The Lancet, 2017. **390**(10113): p. 2673-2734.
2. Tadic, M., C. Cuspidi, and D. Hering, *Hypertension and cognitive dysfunction in elderly: blood pressure management for this global burden.* BMC Cardiovasc Disord, 2016. **16**(1): p. 208.
3. Chan, K.Y., et al., *Epidemiology of Alzheimer's disease and other forms of dementia in China, 1990–2010: a systematic review and analysis.* The Lancet, 2013. **381**(9882): p. 2016-2023.
4. Ward, A., et al., *Mild cognitive impairment: disparity of incidence and prevalence estimates.* Alzheimers Dement, 2012. **8**(1): p. 14-21.
5. Jia, J., et al., *The prevalence of dementia in urban and rural areas of China.* Alzheimers Dement, 2014. **10**(1): p. 1-9.
6. Sierra, C., et al., *Hypertension and mild cognitive impairment.* Curr Hypertens Rep, 2012. **14**(6): p. 548-55.
7. Lazo-Porras, M., et al., *Cognitive impairment and hypertension in older adults living in extreme poverty: a cross-sectional study in Peru.* BMC Geriatr, 2017. **17**(1): p. 250.
8. Zuo, M., et al., *Physical Predictors of Cognitive Function in Individuals With Hypertension: Evidence from the CHARLS Basline Survey.* West J Nurs Res, 2018: p. 193945918770794.
9. Wei, J., et al., *Association between hypertension and cognitive function: A cross-sectional study in people over 45 years old in China.* J Clin Hypertens (Greenwich), 2018. **20**(11): p. 1575-1583.
10. Smith, E.E., et al., *Impaired memory is more closely associated with brain beta-amyloid than leukoaraiosis in hypertensive patients with cognitive symptoms.* PLoS One, 2018. **13**(1): p. e0191345.
11. Goldstein, F.C., A.I. Levey, and N.K. Steenland, *High blood pressure and cognitive decline in mild cognitive impairment.* J Am Geriatr Soc, 2013. **61**(1): p. 67-73.
12. Harrison, J.K., et al., *New horizons: the management of hypertension in people with dementia.* Age and Ageing, 2016. **45**(6): p. 740-746.
13. Gorelick, P.B., 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): p. 2672-713.
14. Haring, B., et al., *Cardiovascular disease and cognitive decline in postmenopausal women: results from the Women's Health Initiative Memory Study.* J Am Heart Assoc, 2013. **2**(6): p. e000369.
15. Liang, X., et al., *Hypertension and High Blood Pressure Are Associated With Dementia Among Chinese Dwelling Elderly: The Shanghai Aging Study.* Front Neurol, 2018. **9**: p. 664.
16. Yuan, J.Q., et al., *Association Between Late-Life Blood Pressure and the Incidence of Cognitive Impairment: A Community-Based Prospective Cohort Study.* J Am Med Dir Assoc, 2018.
17. Corrada, M.M., et al., *Age of onset of hypertension and risk of dementia in the oldest-old: The 90+ Study.* Alzheimers Dement, 2017. **13**(2): p. 103-110.
18. *Alzheimer's Association Update.* Alzheimer's & Dementia, 2017. **13**(10): p. 1181-1184.
19. Peng, S.L., et al., *Age-related changes in cerebrovascular reactivity and their relationship to cognition: A four-year longitudinal study.* Neuroimage, 2018. **174**: p. 257-262.
20. Gulla, C., et al., *Deprescribing antihypertensive treatment in nursing home patients and the effect on blood pressure.* J Geriatr Cardiol, 2018. **15**(4): p. 275-283.
21. Sharifi, F., et al., *Hypertension and Cognitive Impairment: Kahrizak Elderly Study.* International Journal of Gerontology, 2011. **5**(4): p. 212-216.

22. *Alzheimer's Association Update.* Alzheimer's & Dementia, 2018. **14**(12): p. 1674-1675.
23. Lima, N.K.C., *Hypertension and cognition decline: Is there an ultimate link?* J Clin Hypertens (Greenwich), 2018. **20**(11): p. 1584-1586.
24. Luis CA, L.D., Acevedo A, et al., *Mild cognitive impairment: directions for future research.* Neurology, 2003(61): p. 438-444.
25. Chen Jia Ye Zirong, Y.M., Fang Ya, *the Application and Progression of the Montreal Cognitive Assessment in Mild Cognitive Impairment.* Chin J Psychiatr, 2017. **50**(5): p. 386-389.
26. GAO Mingyue, Y.M.K.W.h.Q.P.-y., *Factors and validity analysis of Mini Mental State Examination in Chinese elderly people.* JOURNAL OF PEKING UNIVERSITY(HEALTH SCIENCES) 2015. **47**(3): p. 443-449.
27. Chuanyu, L.F.B.Q.Z.Y.L.H.W., *Quality of life and related factors in patients with major depressive disorde.* Journal of Capital Medical University, 2017. **38**(2): p. 186-191.
28. Wei CHENHu, Z.Q.D.C.W., *Study on the relationship between dementia and plasma homocysteine level.* Pract Geria, 2017. **29**(2): p. 134-136.
29. Yuan Quan, L.X., Yao Wenbin, *the Demandations and factors for long-term care in institutions for disabled elderly.* Chinese Journal of Gerontology, 2017(37): p. 6214-6216.
30. Woolf, C., et al., *Can the Clinical Dementia Rating Scale Identify Mild Cognitive Impairment and Predict Cognitive and Functional Decline?* Dement Geriatr Cogn Disord, 2016. **41**(5-6): p. 292-302.
31. Kjeldsen, S.E., et al., *Intensive blood pressure lowering prevents mild cognitive impairment and possible dementia and slows development of white matter lesions in brain: the SPRINT Memory and Cognition IN Decreased Hypertension (SPRINT MIND) study.* Blood Press, 2018. **27**(5): p. 247-248.
32. Zhu, R.X., X. Liu, and Z.Y. He, *Association between CLU gene rs11136000 polymorphism and Alzheimer's disease: an updated meta-analysis.* Neurological Sciences, 2018. **39**(4): p. 679-689.
33. Hou, X.H., et al., *Models for predicting risk of dementia: a systematic review.* J Neurol Neurosurg Psychiatry, 2018.
34. Jefferson, A.L., et al., *Higher Aortic Stiffness Is Related to Lower Cerebral Blood Flow and Preserved Cerebrovascular Reactivity in Older Adults.* Circulation, 2018. **138**(18): p. 1951-1962.
35. Oishi, E., et al., *Day-to-Day Blood Pressure Variability and Risk of Dementia in a General Japanese Elderly Population: The Hisayama Study.* Circulation, 2017. **136**(6): p. 516-525.
36. Streit, S., R.K.E. Poortvliet, and J. Gussekloo, *Lower blood pressure during antihypertensive treatment is associated with higher all-cause mortality and accelerated cognitive decline in the oldest-old-data from the Leiden 85-plus Study.* Age Ageing, 2018. **47**(4): p. 545-550.
37. Momtaz, Y.A., et al., *Prevalence of hypotension and its association with cognitive function among older adults.* Aging Ment Health, 2018. **22**(4): p. 447-452.
38. van der Wardt, V., et al., *Withdrawal of antihypertensive therapy in people with dementia: feasibility study.* Pilot Feasibility Stud, 2018. **4**: p. 29.
39. Riley, D.E. and A.J. Espay, *Cognitive fluctuations in Parkinson's disease dementia: blood pressure lability as an underlying mechanism.* J Clin Mov Disord, 2018. **5**: p. 1.
40. Petek, B., et al., *Connecting the brain cholesterol and renin-angiotensin systems: potential role of statins and RAS-modifying medications in dementia.* J Intern Med, 2018. **284**(6): p. 620-642.
41. McGuinness, B., et al., *Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia.* Cochrane Database Syst Rev, 2009(4): p. CD004034.
42. Liang, X., et al., *Mental Work Demands and Late-Life Cognitive Impairment: Results From the Shanghai Aging Study.* J Aging Health, 2018: p. 898264318765034.

Tables

Table 1. Follow-up outcomes of hypertensive MCI patients

Variable		MCIp	MCIs	χ2/t	P
Age	<65	25（15.4%）	137（84.6%）	5.538 a	0.019
	≥65	31（27.0%）	84（73.0%）		
HAMD-17 score		2.34±3.42	1.67±2.14	1.406 b	0.165
CDR score		0.75±0.51	0.54±0.35	-4.666b	<0.001
ADL score		18.04±9.05	14.42±2.07	2.973 b	0.004
HIS score		2.96±1.76	2.59±1.07	1.512 b	0.135
Gender	male	14（19.7）	57（80.3）	0.015a	0.904
	female	42（20.4）	164（79.6）		
Singleness	Yes	16（32.0）	34（68.0）	5.252 a	0.022
	No	40（17.6）	187（82.4）		
DM	Yes	17（58.8）	44（41.2）	2.840 a	0.092
	No	39（18.1）	177（81.9）		
BMI	≥28	6（13.0）	42（87.0）	1.006 a	0.605
	24-27.99	28（18.7）	122（81.3）		
	<24	42（17.5）	191（79.6）		
SBP（mmHg）		131.48±12.04	130.41±11.57	0.613b	0.540
DBP（mmHg）		80.09±7.10	79.81±8.69	0.222b	0.824
PP（mmHg）		51.39±12.00	50.60±13.55	0.399b	0.690
Increased PP	Yes	20（19.0）	68（81.0）	0.504 a	0.478
	No	36（22.7）	153（77.3）		
SBP (mmHg)	<120	0	8（100）	2.486a	0.478
	120-139	39（20.7）	149（79.3）		
	140-159	16（21.9）	57（78.1）		
	≥160	1（12.5）	7（87.5）		
DBP (mmHg)	<70	2（22.2）	7（77.8）	0.941 a	0.816
	70-89	44（19.4）	166（80.6）		
	90-109	10（25.0）	30（75.0）		
	≥110	0	1（100）		

MCIp：Mild Cognitive Impairment progression, MCIs：Mild Cognitive Impairment remained stable. DM: Diabetes Mellitus. BMI: Body Mass Index. SBP: Systolic blood pressure. DBP: Diastolic blood pressure, PP: pulse pressure= Systolic minus Diastolic pressure, Increased PP : PP >60mmHg. a：χ2 test, b：t test

Table 2. Follow-up outcomes of hypertensive MCI stratified by age of onset

Variable		<65		χ^2/t	*P*	≥65		χ^2/t	*P*
		MClp	MCls			MClp	MCls		
HAMD-17 score		2.80±4.59	1.69±2.21	1.188[a]	0.245	2.00±2.05	1.64±2.03	0.863[a]	0.390
CDR score		0.66±0.40	0.52±0.34	-2.608[a]	0.009	0.81±0.58	0.56±0.36	-3.559[a]	<0.001
ADL score		17.36±8.50	14.40±1.93	1.733[a]	0.096	18.44±9.46	14.44±2.27	2.368[a]	0.024
HIS score		3.00±1.91	2.65±1.15	0.886[a]	0.383	2.88±1.66	2.53±0.96	1.110[a]	0.274
Gender	male	5（13.5）	32（86.5）			9（26.5）	25（73.5）	1.879[b]	0.170
	female	20（16.0）	105（84.0）			22（27.2）	59（72.8）	3.772[b]	0.052
Singleness	Yes	4（20.0）	16（80.0）			12（40.0）	18（60.0）	2.206[b]	0.137
	No	21（14.8）	121（85.2）			19（22.4）	66（77.6）	2.096[b]	0.148
DM	Yes	10（58.8）	7（41.2）			33（75.0）	11（25.0）	1.543[b]	0.214
	No	15(12.6)	104（87.4）			24（24.7）	73（75.3）	5.321[b]	0.021
BMI	≥28	3（10.0）	27（90.0）			3（30.0）	7（70.0）	2.353[b]	0.125
	24-27.99	11（16.2）	57（83.8）			14（31.8）	30（68.2）	3.770[b]	0.052
	<24	11（17.2）	53（82.8）			14（23.0）	47（77.0）	0.648[b]	0.421
SBP (mmHg)		131.92±13.20	131.01±12.43	0.332[a]	0.740	130.78±11.22	129.55±10.02	0.543[a]	0.590
DBP (mmHg)		80.40±5.94	80.90±9.34	-0.257[a]	0.798	79.84±7.88	78.12±7.21	1.125[a]	0.263
PP (mmHg)		51.52±11.02	50.12±15.44	0.434[a]	0.665	51.29±12.91	51.39±9.76	-0.040[a]	0.968
Increased PP	Yes	8（15.4）	44（84.6）			12（33.3）	24（66.7）	3.902[b]	0.048
	No	17（15.5）	93（84.5）			19（24.1）	60（75.9）	2.203[b]	0.138

MClp：Mild Cognitive Impairment progressed to dementia, MCls：Mild Cognitive Impairment remained stable. DM: Diabetes Mellitus. BMI: Body Mass Index. SBP: Systolic blood pressure. DBP: Diastolic blood pressure, PP: pulse pressure = Systolic minus Diastolic pressure, Increased PP: PP >60mmHg. [a]：t test, [b]：χ^2 test

Table 3. The variables assignment of Multivariate logistic regression analysis

Variable	Factors	Assignment
X1	Gender	Male=1, Female=2
X2	Educational level	<12 years=1, ≥12 years=2
X3	Singleness	Yes=1, No=2
X4	Occupation	Mental labor=1, Physical labor =2
X5	Diabetes Mellitus	Yes=1, No=2
X6	Hyperlipidemia	Yes =1, No =2
X7	Smoking	Yes =1, No =2
X8	Alcohol Consumption	Yes =1, No =2
X9	History of Dementia	Yes =1, No =2
X10	Hypertension alone	Yes =1, No =2
X11	Increased pulse pressure	Yes =1, No =2
X12	Hypertension age of onset	<65 years=1, ≥65 years=2

Table 4. Results of multivariate logistic regression

	β	S.E.	*P*	OR	95% C.I. of OR	
					Lower limit	Upper limit
Gender	-0.395	0.508	0.437	0.673	0.249	1.823
Education level	0.059	0.964	0.951	1.061	0.160	7.020
Age	-0.324	0.166	0.029*	0.723	0.502	0.964
Singleness	-0.440	0.487	0.367	0.644	0.248	1.673
Occupation	-0.683	0.590	0.247	0.505	0.159	1.604
Number of children	0.417	0.240	0.082	1.517	0.949	2.428
Diabetes Mellitus	0.250	0.549	0.649	1.284	0.438	3.766
Hyperlipidemia	-1.508	1.053	0.152	0.221	0.028	1.744
Smoking	0.243	1.001	0.808	1.275	0.179	9.078
Alcohol Consumption	-0.803	1.135	0.479	0.448	0.048	4.146
History of Dementia	0.946	0.950	0.320	2.575	0.400	16.573
BMI	-0.254	0.301	0.400	0.776	0.430	1.401
Hypertension alone	0.449	0.471	0.341	1.567	0.622	3.949
Systolic Pressure	-0.059	0.489	0.904	0.943	0.361	2.457
Diastolic Pressure	0.194	0.474	0.682	1.214	0.480	3.072
Increased pulse pressure	0.068	0.431	0.874	1.070	0.460	2.490
Hypertension age of onset	0.218	0.375	0.561	1.244	0.596	2.596

* $p < 0.05$