Prospective Study of Arterial Stiffness and Subsequent Cognitive Decline Among Community-Dwelling Older Japanese

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ABSTRACT

Background: Brachial-ankle pulse wave velocity (baPWV) is inversely associated with cognitive function. However, it is not known whether baPWV predicts cognitive decline (CD) in later life. We examined whether or not baPWV is an independent risk marker of subsequent CD in a population of older Japanese.

Methods: Among 982 adults aged 65 years or older who participated in a baseline survey, 526 cognitively intact adults (Mini-Mental State Examination [MMSE] score ≥24; mean [SD] age, 71.7 [5.6] years; women, 57.8%) were followed for a period of up to 5 years. Pulse wave velocity was determined using an automated waveform analyser. Cognition was assessed by the MMSE, and CD was defined as a decrease of two points or more on the MMSE.

Results: During an average follow-up of 3.4 years, 85 participants (16.2%) developed CD. After controlling for important confounders, the odds ratios for CD in the highest and middle tertiles of baPWV, as compared with the lowest tertile, were 2.95 (95% confidence interval, 1.29–6.74) and 2.39 (95% confidence interval, 1.11–5.15), respectively.

Conclusions: High baPWV was an independent predictor of CD in a general population of older adults and may be useful in the clinical evaluation of elders.

Key words: cognitive decline; arterial stiffness; older persons

INTRODUCTION

Dementia is a growing public health concern worldwide. The World Health Organization estimates that the number of people with dementia will double by 2030 and more than triple by 2050.¹ Dementia is a major cause of disability and need for premature care in older adults. It also affects the wellbeing of caregivers, who experience physical and mental stress during care, and is an economic burden due to the costs associated with providing social care. Alzheimer’s disease (AD) causes long-term pathological changes, and previous studies noted an association between the prodromal stage of AD and cognitive decline (CD). Wilson and colleagues² reported that, compared with a group with no cognitive impairment, the annual rate of CD was more than doubled in a group with mild cognitive impairment and more than quadrupled in a group with AD. There is no established treatment for dementia; however, prevention or delay of CD might assist in limiting the onset of future dementia.

We previously reported several independent risk markers in CD incidence, including lower physical performance³ and nutritional biomarkers.⁴ Moreover, arterial stiffness (loss of cushioning capacity) was recently used as risk factor for CD in epidemiological and clinical studies. Arterial stiffness is associated with physical activity and nutritional status, is a marker of functional and structural changes in arteries, and can be assessed noninvasively using pulse wave velocity (PWV) measurement.⁵ Previous studies used carotid-femoral PWV (cfPWV), which measures the velocity of the pulse wave as it travels a given distance between the carotid and femoral arteries⁶ and reflects the stiffness of elastic arteries.⁷ A high cfPWV was significantly associated with marked declines in psychomotor speed,⁸ verbal learning, and nonverbal memory⁹ in older adults. Scuteri and colleagues¹⁰,¹¹ reported an association between cfPWV and...
CD among older adults who reported memory problems and were assessed using the Mini-Mental State Examination (MMSE). However, no independent association was found between cfPWV and CD in the Rotterdam Study.12

Although cfPWV is regarded throughout the world as the gold standard for measurement of arterial stiffness, brachial-ankle PWV (baPWV) measurement is more frequently used in Japan.7 This method was developed to assess pulse wave transmission between the brachial and tibial arteries13 and reflects stiffness in both muscular and elastic arteries.7 The baPWV technique has good reproducibility, even when not performed by highly skilled technicians, and is not time-consuming. Earlier cross-sectional studies found that baPWV was inversely associated with cognitive function among Japanese aged 70 years or older14 and 85 years.5 However, the longitudinal association between baPWV and CD has not been investigated among community-dwelling elderly individuals. Furthermore, whether or not arterial stiffness is associated with CD after adjustment for sociomedical factors is unknown.

A better understanding of the relation of arterial stiffness to CD risk might yield new insights regarding physiological mechanisms during the prodromal stage of dementia. In this prospective study of community-dwelling older adults, we measured baPWV and health-related factors, including measures of physical performance, nutritional biomarkers, chronic diseases, and apolipoprotein E (APOE) genotype, at baseline. We then used the MMSE to follow the cognitive function of participants. The objective of the study was to determine whether baPWV was independently associated with CD after adjustment for potential confounders.

METHODS

Participants

Data were collected as part of a comprehensive health examination conducted in Kusatsu Town, Gunma Prefecture, Japan. In addition to an annual preventive health check-up, for residents aged 40 years or older, participants aged 65 years or older underwent a geriatric assessment that included measurement of baPWV and cognitive function. The details of the study design have been previously reported.3,4 All participants provided written informed consent under conditions approved by the Ethics Committee at Tokyo Metropolitan Institute of Gerontology. Baseline assessments were performed from 2008 through 2011 at the same local public health center. Annual follow-up assessments were conducted in the same manner from 2012 through 2013. To be eligible for the study, individuals had to complete the baseline assessment at least once. Among the 2313 elders with valid and complete baseline data, 982 were selected for participation in the present study. Ultimately, data from 526 adults who had completed both baseline and follow-up assessments were analyzed, as shown in Figure 1. The reasons for attrition during the follow-up period (n = 456) were operationally defined as mild cognitive impairment at baseline (MMSE score <24; n = 29), death (n = 59), need for care under the Long-term Care Insurance program (n = 65), relocation (n = 52), and unknown reasons (n = 251).

Brachial-ankle pulse wave velocity

The baPWV (cm/sec) was measured with an automatic waveform analyzer (BP-203 RPE III; Omron Colin Co., Ltd., Tokyo, Japan). This technique has been described in detail elsewhere.14–18 Briefly, cuffs wrapped around the brachia and ankles were connected to a plethysmographic sensor, which determined the volume pulse form, and an oscillometric pressure sensor. Pressure waveforms were recorded simultaneously at the brachial and tibial arteries to determine the time interval between the initial rise in the brachial and tibial waveforms. The path length from the suprasternal notch to the elbow (ΔDa) was obtained from superficial measurements and was estimated using the equation ΔDa = 0.2195 × H2 – 2.0734, where H is the height of the participant in centimeters. The path length from the suprasternal notch to the ankle (ΔDb) was calculated as ΔDb = (0.5643 × H2 – 18.3810) + (0.2486 × H – 30.7090). The baPWV was calculated as the mean of the values from the left and right sides, and the data were divided into tertiles (≤1591, 1591–1889, and ≥1889 cm/s) in the analysis.

Cognitive function

Cognitive function was assessed using the MMSE, which was administered by well-trained personnel.3,4 The score ranges from 0 to 30, with lower scores indicating poorer global cognitive function. A decrease of at least two points on the MMSE during the follow-up period was defined as CD.19–21

Laboratory data

Blood testing included white blood cell (WBC) count, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, hemoglobin A1c, total cholesterol, high-density lipoprotein cholesterol, triglycerides, creatinine, and albumin. Nonfasting blood samples were collected using standard procedures. Samples were analyzed at the Sannaiakai Clinic, which is regularly monitored by several domestic authorities. APOE genotyping was performed on coded DNA specimens by technicians blinded to the diagnosis. The categorical variable APOE was classified by genotype as ε2ε2, ε2ε3, ε2ε4, ε3ε3, ε3ε4, and ε4ε4.22

Other variables

The covariates included sex, age, years of education, living arrangement, frequency of going outdoors, history of chronic diseases and antihypertensive drug use,23 body height and weight, body mass index (BMI), resting blood pressure, ankle-brachial pressure index (ABI), grip strength, usual and maximum gait speeds, Tokyo Metropolitan Institute of
Gerontology Index of Competence (TMIG-IC), Geriatric Depression Scale (GDS) Short-version, and years of follow-up. Well-trained personnel interviewed the participants.

Chronic diseases included clinically relevant medical conditions: hypertension, hyperlipidemia, cerebral vascular disease (stroke, cerebral hemorrhage, and subarachnoid hemorrhage), heart disease (angina, myocardial infarction, arrhythmia, and others), and diabetes mellitus. For each condition, participants were asked whether a physician had diagnosed the specific condition (yes or no).

Grip strength (kg) was measured in the dominant hand using a standard hydraulic handgrip dynamometer; participants were asked to squeeze the handle as hard as they could. Gait speed was measured over a straight 11-m walkway marked with tape at 3 m and 8 m. Participants were asked to walk at their usual and maximum pace, and well-trained staff measured the time required to walk 5 m and calculated gait speed (expressed as m/sec). Usual gait performance was measured once. Grip strength and maximum gait speed were measured twice, and the better of the two results was recorded.

The TMIG-IC \(^{27}\) was designed to measure higher-level competence in older community residents. The score ranges from 0 to 13, with higher scores indicating higher functional capacity.

**Statistical analyses**

The Mann-Whitney \(U\) test and chi-square test were used to compare baseline sociomedical characteristics between individuals who developed CD during follow-up and those who did not. We used logistic regression plot to predict the probability of occurrence for subsequent CD with baPWV adjusted for sex, age, and follow-up year. The dataset for the present study does not include censored data, and the effect of baPWV at baseline on subsequent CD would not change during the follow-up period. Thus, we used multiple logistic regression models to examine independent associations between measures of baPWV at baseline with subsequent CD. We adjusted for confounding factors using multiple logistic regression models in which baPWV was defined as the independent variable, and subsequent CD was defined as the dependent variable. Some continuous variables were divided into tertiles as a covariate.

Four models were used. The first was the crude model (model 1). In the second, the covariates were sex, age, and follow-up year (model 2). Model 3 included the covariates

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Figure 1. Study flow according to cognitive outcome.

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Completed assessment in 2008, \(n=616\)
Completed assessment in 2009, \(n=586\)
Completed assessment in 2010, \(n=519\)
Completed assessment in 2011, \(n=592\)

Selected for first-time assessment \(n=982\)

Excluded, \(n=456\)
- Mild cognitive impairment at baseline (MMSE < 24), \(n=29\)
- Died, \(n=59\)
- Recipients of care under Long-term Care Insurance program, \(n=65\)
- Relocated outside study area, \(n=52\)
- Alive, but did not participate in follow-up, \(n=251\)

\(\geq 1\) follow-up MMSE in 2012 or 2013, \(n=526\)

Cognitive decline, \(n=85\)
No cognitive decline, \(n=441\)
in model 2 plus all factors that were significantly associated with CD in univariate analysis. In model 4, antihypertensive medication, systolic blood pressure, high-density lipoprotein cholesterol, albumin, and APOE genotype were added as important covariates. We excluded some factors, to avoid multicollinearity among covariates. The statistical models were run separately. Statistics were computed using SPSS (version 18.0; SPSS, Inc., Chicago, IL, USA) and SAS (version 9.4; SAS Institute, Inc., Cary, NC, USA), and the level of significance was set at \( P < 0.05 \).

RESULTS

Among study participants at baseline, average (standard deviation [SD]) age was 71.7 (5.6) years, 57.8% were women, 22.5% lived alone, 13.2% had 13 or more years of education, 54.8% had maximum scores on the TMIG-IC, and 87.3% had a score of 26 or higher on the MMSE. Chronic diseases included clinically relevant medical conditions; 36.3% had hypertension (33.5% used antihypertensive drugs), 21.5% had hyperlipidemia, 4.0% had cerebral vascular disease, 11.4% had heart disease, and 10.3% had diabetes. The average (SD) baPWV (cm/sec) was 1782 (379).

During a mean follow-up of 3.4 years, 85 of 526 (16.2%) adults developed CD. Table 1 shows the baseline demographic and health characteristics of individuals who did and did not develop CD during the follow-up period. At baseline, participants who developed CD were older, had fewer years of education, were less likely to go outdoors, had lower usual and maximum gait speeds, had higher WBC counts, had higher MMSE scores, and had longer duration of follow-up compared to participants who did not develop CD; all of these variables were included as potential confounders in multivariate analysis.

Figure 2 clearly shows that the probability of CD occurrence increased with increasing baPWV, after controlling for sex, age, and duration of follow-up. Table 2 shows the associations of baPWV with CD, after controlling for potential confounders, in the four statistical models. Among the highest and middle tertiles of baPWV, the odds ratios (ORs) for CD were 3.88 (95% confidence interval [CI], 1.99–7.54) and 2.61 (95% CI, 1.32–5.18), respectively, compared with participants in the lowest tertile in the unadjusted model (model 1). After controlling for factors that were significantly associated with CD in univariate analysis (excluding maximum gait speed) (model 3), the corresponding ORs were 2.76 (95% CI, 1.30–5.84) and 2.35 (95% CI, 1.12–4.95). Furthermore, when potential confounders for CD were added to the model (model 4), baPWV remained independently significant: participants in the highest and middle tertiles of baPWV had ORs of 2.95 (95% CI, 1.29–6.74) and 2.39 (95% CI, 1.11–5.15), respectively, for CD.

**DISCUSSION**

Recent cross-sectional studies\(^5\)\(^4\) reported an association between baPWV and cognitive function; however, the longitudinal association with CD has not previously been studied. The present prospective study of community-dwelling older Japanese is the first to show that baPWV is an independent predictor of CD, as assessed by MMSE, after adjusting for potential confounders.
Studies have revealed several pathways between arterial stiffness and cognitive function. Most importantly, higher blood pressure level may have a key role in CD. In the present study, baPWV was independently associated with CD after adjustment for blood pressure level and use of antihypertensive medication. Furthermore, one study found that a baPWV value in the highest quartile was a significant predictor of progression to higher blood pressure categories, which suggests that arterial stiffness develops before hypertension.

Figure 2. Logistic regression plot shows the relationship between brachial-ankle pulse wave velocity (baPWV) at baseline and the probability of occurrence for subsequent cognitive decline (solid line) adjusted for sex, age, and follow-up year, with 95% confidence intervals (gray) among community-dwelling Japanese aged ≥65 years.

Table 2. Independent associations of brachial-ankle pulse wave velocity at baseline with subsequent cognitive decline in community-dwelling Japanese aged ≥65 years

| Independent variable                  | Model 1 (n = 524) | Model 2 (n = 524) | Model 3 (n = 487) | Model 4 (n = 483) |
|---------------------------------------|-------------------|-------------------|-------------------|-------------------|
| PWV tertile                           |                   |                   |                   |                   |
| lowest (reference)                    | 1                 | 1                 | 1                 | 1                 |
| middle                                | 2.61 (1.32–5.18)**| 2.44 (1.21–4.90)* | 2.35 (1.12–4.95)* | 2.39 (1.11–5.15)* |
| highest                               | 3.88 (1.99–7.54)**| 2.90 (1.44–5.86)**| 2.76 (1.30–5.84)**| 2.95 (1.29–6.74)**|
| Female sex                            | 1.15 (0.74–1.88)  | 0.92 (0.54–1.57)  | 0.99 (0.57–1.73)  |                   |
| Age, per year                         | 1.06 (1.02–1.11)* | 1.04 (0.99–1.09)  | 1.05 (0.99–1.10)  |                   |
| Duration of follow-up, per year       | 1.51 (1.14–2.01)* | 1.45 (1.05–2.00)* | 1.55 (1.11–2.16)**|                   |
| ≥13 years of education                |                   |                   |                   |                   |
| Going outdoors more than once a day   |                   |                   |                   |                   |
| Usual walking speed, per tertile increase |                   |                   |                   |                   |
| White blood cell count, per tertile increase |                   |                   |                   |                   |
| MMSE ≥26 points                       |                   |                   |                   |                   |
| Use of antihypertensive medication    |                   |                   |                   | 0.77 (0.43–1.38)  |
| Systolic blood pressure, per tertile increase | 1.06 (0.75–1.52) |                   |                   |                   |
| HDL cholesterol, per tertile increase | 0.82 (0.59–1.15)  |                   |                   |                   |
| Albumin, per tertile increase         | 1.00 (0.78–1.33)  |                   |                   |                   |
| APOE genotype, ε4                     | 0.85 (0.42–1.72)  |                   |                   |                   |

APOE, apolipoprotein E; CI, confidence interval; HDL, high-density lipoprotein; OR, odds ratio; PWV, pulse wave velocity; MMSE, Mini-Mental State Examination.

*P < 0.05, **P < 0.01.

Tertiles were defined as follows: usual walking speed (m/s): ≤1.29, 1.29–1.47, ≥1.47; white blood cell count (/µL): ≤4700, 4700–5800, ≥5800; systolic blood pressure (mm Hg): ≤121, 121–137, ≥137; HDL cholesterol (mg/dL): ≤51, 51–63, ≥63; albumin (g/dL): ≤4, 4–4.3, ≥4.3.
The present evidence suggests two mechanisms by which baPWV may predict CD development through higher blood pressure. First, blood flow disturbance may contribute to CD. Lower arterial elasticity leads to hypertension, which might accelerate narrowing of cerebral vasculature, leading to chronic hypoperfusion and ischemia. The resulting state of chronic hypoperfusion may impede delivery of energy substrates and nutrients to active brain cells and directly injure cerebral white matter or allow toxic metabolic byproducts to accumulate within the brain and blood vessels. In addition, ischemia may lead to accumulation of amyloid precursor protein and accelerated formation of free oxygen radicals, as has been seen in animal experiments.

Second, certain diseases might have mediating roles in the pathophysiology of CD. Hypertension induced by artherosclerosis may lead to thickening of the cerebrovascular endothelium and endothelial dysfunction and contribute to thrombosis and microinfarcts. Moreover, dysfunction in the blood-brain barrier could be important in CD. Concurrent breakdown of the blood-brain barrier may allow toxins, proteases, or other substances in the blood to enter the brain interstitial space and injure surrounding neurons and glial cells. Other studies have reported a significant positive relationship between arterial stiffness and volume or localization of white matter lesions, a known predisposing factor for dementia. A higher PWV was significantly associated with a greater volume of white matter hyperintensities on neuroimaging.

The incidence rate of CD was 16.2% during a mean follow-up of 3.4 years. This value is compatible with previous results. In univariate analysis, CD was closely associated with age, years of education, frequency of going outdoors, usual and maximum gait speeds, WBC count, MMSE score, years of follow-up, and baPWV, and marginally associated with systolic blood pressure and pulse pressure. Andrew and colleagues found that increasing social vulnerability was associated with CD, and Saczynski and colleagues reported that a decline in social engagement between mid- and late-life was predictive of incident dementia. Further research is thus needed to explore the associations of social factors, such as frequency of going outdoors, with CD. Our findings support previous results on gait and cognitive function. Although a cross-sectional study found an inverse association between WBC count and psychomotor cognitive performance in the elderly, longitudinal associations have not been examined. Further study is necessary to examine the independent association of WBC count with CD, after controlling for cytokines and factors derived from leucocytes. In previous studies, the association between higher MMSE scores and CD was attributed to a ceiling effect. Several studies have shown that the ε4 allele is a risk factor for cognitive impairment and decline; however, no studies found an effect of APOE genotype on cognitive functioning.

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REFERENCES

1. World Health Organization. Dementia a public health priority. http://whqlibdoc.who.int/publications/2012/9789241564458_eng.pdf.
2. Wilson RS, Aggarwal NT, Barnes LL, Mendes de Leon CF, Hebert LE, Evans DA. Cognitive decline in incident Alzheimer disease in a community population. Neurology. 2010;74:951–5.

3. Taniguchi Y, Yoshida H, Fujiwara Y, Motohashi Y, Shinkai S. A prospective study of gait performance and subsequent cognitive decline in a general population of older Japanese. J Gerontol A Biol Sci Med Sci. 2012;67:796–803.

4. Taniguchi Y, Shinkai S, Nishi M, Murayama H, Nofuji Y, Yoshida H, et al. Nutritional biomarkers and subsequent cognitive decline among community-dwelling older Japanese: a prospective study. J Gerontol A Biol Sci Med Sci. 2014;69:1276–83.

5. Fukuhara M, Matsumura K, Ansai T, Takata Y, Sonoki K, Akifusa S, et al. Prediction of cognitive function by arterial stiffness in the very elderly. Circ J. 2006;70:756–61.

6. Hanon O, Haulon S, Lenoir H, Seux ML, Rigaud AS, Safar M, et al. Relationship between arterial stiffness and cognitive function in elderly subjects with complaints of memory loss. Stroke. 2005;36:2193–7.

7. Ueda I, Tagawa T, Watanabe S, Yamakawa K, Yasu T, Ueda S. Comparability and reproducibility of the carotid-femoral pulse wave velocity measurements using a multi-element carotid tonometry sensor. J Hum Hypertens. 2008;22:699–703.

8. Watson NL, Sutton-Tyrrell K, Rosano C, Boudreau RM, Hardy Volpe M. Arterial stiffness as an independent predictor of cognitive decline among well-functioning older adults. J Gerontol A Biol Sci Med Sci. 2011;66:1336–42.

9. Waldstein SR, Rice SC, Thayer JF, Najjar SS, Scuteri A, Zonderman AB. Pulse pressure and pulse wave velocity are related to cognitive decline in the Baltimore Longitudinal Study of Aging. Hypertension. 2008;51:99–104.

10. Scuteri A, Tesauro M, Appolloni S, Preziosi F, Brancati AM, Volpe M. Arterial stiffness as an independent predictor of longitudinal changes in cognitive function in the older individual. J Hypertens. 2007;25:1035–40.

11. Scuteri A, Tesauro M, Gugliini L, Lauro D, Fini M, Di Daniele N. Aortic stiffness and hypertension episodes are associated with impaired cognitive function in older subjects with subjective complaints of memory loss. Int J Cardiol. 2013;169:371–7.

12. Poels MM, van Oijen M, Mattace-Raso FU, Hofman A, Koudstaal PJ, Wittener JC, et al. Arterial stiffness, cognitive decline, and risk of dementia: the Rotterdam study. Stroke. 2007;38:888–92.

13. Fujiwara Y, Chaves P, Takahashi R, Amano H, Kumagai S, Fujita K, et al. Relationships between brachial-ankle pulse wave velocity and conventional atherosclerotic risk factors in community-dwelling people. Prev Med. 2004;39:1135–44.

14. Fujiwara Y, Chaves P, Takahashi R, Amano H, Yoshida H, Kumagai S, et al. Arterial pulse wave velocity as a marker of poor cognitive function in an elderly community-dwelling population. J Gerontol A Biol Sci Med Sci. 2005;60:607–12.

15. Yamashina A, Tomiyama H, Takeda K, Tsuda H, Arai T, Hirose K, et al. Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. Hypertens Res. 2002;25:359–64.

16. Tomiyama H, Yamashina A, Arai T, Hirose K, Koji Y, Chikamori T, et al. Influences of age and gender on results of noninvasive brachial-ankle pulse wave velocity measurement—a survey of 12 517 subjects. Atherosclerosis. 2003;166:303–9.

17. Suzuki E, Kashiwagi A, Nishio Y, Egawa K, Shimizu S, Maegawa H, et al. Increased arterial wall stiffness limits flow volume in the lower extremities in type 2 diabetic patients. Diabetes Care. 2001;24:2107–14.

18. Ohnishi H, Saitoh S, Takagi S, Ohata J, Isobe T, Kikuchi Y, et al. Pulse wave velocity as an indicator of atherosclerosis in impaired fasting glucose: the Tanno and Sobetsu study. Diabetes Care. 2003;26:437–40.

19. Heude B, Ducimetière P, Berr C; EVA Study. Cognitive decline and fatty acid composition of erythrocyte membranes—The EVA Study. Am J Clin Nutr. 2003;77:803–8.

20. Kalmijn S, Feskens EJ, Launer LJ, Kromhout D. Polyunsaturated fatty acids, antioxidants, and cognitive function in very old men. Am J Epidemiol. 1997;145:33–41.

21. Ng TP, Niti M, Feng L, Kua EH, Yap KB. Albumin, apolipoprotein E-epsilon4 and cognitive decline in community-dwelling Chinese older adults. J Am Geriatr Soc. 2009;57:101–6.

22. Yip AG, Brayne C, Easton D, Rubinszttein DC; Medical Research Council Cognitive Function Ageing Study (MRC CFAS). Apolipoprotein E4 is only a weak predictor of dementia and cognitive decline in the general population. J Med Genet. 2002;39(9):639–43.

23. Levi Marpillat N, Macquin-Mavier I, Tropeano AI, Bachoud-Levi AC, Maison P. Antihypertensive classes, cognitive decline and incidence of dementia: a network meta-analysis. J Hypertens. 2013;31:1073–82.

24. Deary IJ, Whalley LJ, Batty GD, Starr JM. Physical fitness and lifetime cognitive change. Neurology. 2006;67:1195–200.

25. Shinkai S, Watanabe S, Kumagai S, Fujiwara Y, Amano H, Yoshida H, et al. Walking speed as a good predictor for the onset of functional dependence in a Japanese rural community population. Age Ageing. 2000;29:441–6.

26. Nagasaki H, Itoh H, Hashizume K, Furuta T, Maruyama H, Kinugasa T. Walking patterns and finger rhythm of older adults. Percept Mot Skills. 1996;82:435–47.

27. Koyano W, Shibata H, Nakazato K, Haga H, Suyama Y. Measurement of competence: reliability and validity of the TMIG Index of Competence. Arch Gerontol Geriatr. 1991;13:103–16.

28. Launer LJ, Masaki K, Petrovitch H, Foley D, Havlik RJ. The association between midlife blood pressure levels and late-life cognitive function. The Honolulu-Asia Aging Study. JAMA. 1995;274:1846–51.

29. Kiwipello M, Helkala EL, Hänninen T, Laakso MP, Hallikainen M, Alhainen K, et al. Midlife vascular risk factors and late-life mild cognitive impairment: A population-based study. Neurology. 2001;56:1683–9.

30. Kilander L, Nyman H, Boberg M, Hansson L, Lithell H. Hypertension is related to cognitive impairment: a 20-year follow-up of 999 men. Hypertension. 1998;31:780–6.

31. Elias MF, Wolf PA, D’Agostino RB, Cobb J, White LR. Untreated blood pressure level is inversely related to cognitive functioning: the Framingham Study. Am J Epidemiol. 1993;138:353–64.

32. Yambe M, Tomiyama H, Yamada J, Koji Y, Motobe K, Shina K, et al. Arterial stiffness and progression to hypertension in...
Japanese male subjects with high normal blood pressure. J Hypertens. 2007;25:87–93.
33. Liao D, Arnett DK, Tyroler HA, Riley WA, Chambless LE, Szkoł M, et al. Arterial stiffness and the development of hypertension. The ARIC study. Hypertension. 1999;34:201–6.
34. Iadecola C, Park L, Capone C. Threats to the mind: aging, amyloid, and hypertension. Stroke. 2009;40(3 Suppl):S40–4.
35. Skoog I, Gustafson D. Hypertension and related factors in the etiology of Alzheimer’s disease. Ann N Y Acad Sci. 2002;977:29–36.
36. Nichols W, O’Rourke MF, McDonald DA. McDonald’s Blood Flow in the Arteries: Theoretical, Experimental, and Clinical Principles. 5th ed. New York: Oxford University Press; 2005.
37. Wardlaw JM, Sandercock PA, Dennis MS, Starr J. Is breakdown of the blood-brain barrier responsible for lacunar stroke, leukoaraiosis, and dementia? Stroke. 2003;34:806–12.
38. Henskens LH, Kroon AA, van Oostenbrugge RJ, Gronenschild EH, Fuss-Lejeune MM, Hofman PA, et al. Increased aortic pulse wave velocity is associated with silent cerebral small-vessel disease in hypertensive patients. Hypertension. 2008;52:1120–6.
39. Kearney-Schwartz A, Rossignol P, Bracard S, Felblinger J, Fay R, Boivin JM, et al. Vascular structure and function is correlated to cognitive performance and white matter hyperintensities in older hypertensive patients with subjective memory complaints. Stroke. 2009;40:1229–36.
40. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American heart association/American stroke association. Stroke. 2011;42:2672–713.
41. Andrew MK, Rockwood K. Social vulnerability predicts cognitive decline in a prospective cohort of older Canadians. Alzheimers Dement. 2010;6(4):319–25.e1.
42. Szczynski JS, Pfeifer LA, Masaki K, Korfi ES, Laurin D, White L, et al. The effect of social engagement on incident dementia: the Honolulu-Asia Aging Study. Am J Epidemiol. 2006;163:433–40.
43. Kao TW, Chang YW, Chou CC, Hu J, Yu YH, Kuo HK. White blood cell count and psychomotor cognitive performance in the elderly. Eur J Clin Invest. 2011;41:513–20.
44. Yasuno F, Tanimukai S, Sasaki M, Ikejima C, Yamashita F, Kodama C, et al. Effect of plasma lipids, hypertension and APOE genotype on cognitive decline. Neurobiol Aging. 2012;33:2633–40.
45. Bremsky P, Guralnik JM, Launer L, Albert M, Seeman TE; MacArthur Studies of Successful Aging. The role of APOE-epsilon4 in longitudinal cognitive decline: MacArthur Studies of Successful Aging. Neurology. 2003;60(7):1077–81.
46. Howieson DB, Camicioli R, Quinn J, Silbert LC, Care B, Moore MM, et al. Natural history of cognitive decline in the old old. Neurology. 2003;60(9):1489–94.
47. Bathum L, Christiansen L, Jeune B, Vaupel J, McGue M, Christensen K. Apolipoprotein e genotypes: relationship to cognitive functioning, cognitive decline, and survival in nonagenarians. J Am Geriatr Soc. 2006;54:654–8.
48. Hyman BT, Gomez-Isla T, Briggs M, Chung H, Nichols S, Kohout F, et al. Apolipoprotein E and cognitive change in an elderly population. Ann Neurol. 1996;40:55–66.
49. Small BJ, Graves AB, McEvoy CL, Crawford FC, Mullan M, Mortimer JA. Is APOE—epsilon4 a risk factor for cognitive impairment in normal aging? Neurology. 2000;54:2082–8.
50. Nichols W, O’Rourke MF. McDonald’s Blood Flow in the Arteries: Theoretical, Experimental, and Clinical Principles. 4th ed. London, U.K.: Edward Arnold; 1998.
51. Pinsky PF, Miller A, Kramer BS, Church T, Reding D, Prorok P, et al. Evidence of a healthy volunteer effect in the prostate, lung, colorectal, and ovarian cancer screening trial. Am J Epidemiol. 2007;165(8):874–81.
52. Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson Ö, et al. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility—Reykjavik study. Brain. 2011;134(Pt 11):3398–407.