Association between the Cardio-Ankle Vascular Index and Executive Function in Community-Dwelling Elderly People

Taiki Sugimoto1, 2, 3, Shogo Misu4, Ryuichi Sawa3, Sho Nakakubo3, 5 Yuya Ueda3, Nobuyuki Nakatsu3, Takashi Saito3, Ryo Nakamura3, Shunsuke Murata3 and Rei Ono3

1Center for Comprehensive Care and Research on Memory Disorders, National Center for Geriatrics and Gerontology, Obu, Japan
2Medical Genome Center, National Center for Geriatrics and Gerontology, Obu, Japan
3Department of Community Health Sciences, Kobe University Graduate School of Health Sciences, Kobe, Japan
4Kobe City Hospital Organization, Kobe City Medical Center West Hospital, Kobe, Japan
5Department of Preventive Gerontology, Center for Gerontology and Social Science, National Center for Geriatrics and Gerontology, Obu, Japan

Aim: The aim of this study was to investigate the cross-sectional association between arterial stiffness (AS) measured with the cardio-ankle vascular index (CAVI) and executive function in community-dwelling elderly people.

Methods: Subjects were 140 community-dwelling elderly people who participated in the study at Kobe, Japan during the period of August–September 2014, of which 126 (mean age ± SD: 73.2 ± 6.1, female: 67.5%) met the inclusion criteria and completed the study. Age, sex, body mass index, global cognition, existence of chronic disease, medication, smoking history, and years of education were assessed. The degree of AS was assessed using CAVI. Executive function was assessed using the Category Word Fluency Test (CWFT), Letter Word Fluency Test (LWFT), and Digit Symbol Substitution Test (DSST). We used a correlation analysis and multiple linear regression analysis to investigate whether higher CAVI was independently associated with lower executive function.

Results: In the univariate analysis, higher mean CAVI correlated with lower CWFT ($\rho = -0.21$, $p = 0.020$), LWFT ($\rho = -0.32$, $p < 0.001$), and DSST ($\rho = -0.31$, $p < 0.001$). In the multivariate analysis, higher mean CAVI was associated with lower LWFT ($\beta = -0.21$, $p = 0.046$) after adjusting for confounding factors, although there was no association with CWFT ($\beta = -0.05$, $p = 0.61$) and DSST ($\beta = -0.06$, $p = 0.51$).

Conclusions: We found that high CAVI was associated with lower LWFT. These results suggest that arterial stiffness is associated with lower performance in phonemic fluency.

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Key words: Executive function, Arterial stiffness, Community-dwelling elderly people

Introduction

Cognitive abilities decline with normal aging, particularly in the domains of executive function1. Executive function is a cognitive ability that involves the planning and execution of goal-directed behaviors, abstract reasoning, and judgment2. Several studies suggest that lower executive function is a risk factor for falls in community-dwelling elderly people3. Another longitudinal study found that lower baseline scores on the measures of executive function predicted the dependence of ADL and IADL and increased mortality over 6 years4. Preventing the decline of executive function is important in preventing falls and performing ADL and IADL independently in older...
Increased arterial stiffness is observed in patients with cardiovascular risk factors, such as hypertension, dyslipidemia, and diabetes mellitus, and these factors have been recognized as playing an important role in the vascular pathogenesis of cognitive decline. Recent studies have reported the association of these factors with lower executive function. Although the association between increased arterial stiffness and lower executive function has been examined, the association remains controversial. In a cross-sectional study of community-dwelling elderly people, arterial stiffness measured according to the aortic pulse wave velocity (PWV) was found to be associated with lower executive function. Conversely, another cross-sectional study demonstrated that carotid to femoral PWV was not associated with executive function. Similarly, a longitudinal study found that carotid to femoral PWV was not a risk factor for the decline of executive function.

Although PWV is widely used for measuring arterial stiffness, there are several problems associated with the measurement. First, measurement of PWV may be affected by stress. Second, measurement of PWV is affected by the blood pressure (BP) at the time of measurement. Therefore, it is difficult to evaluate arterial stiffness in patients treated with antihypertensive medication.

Recently, the cardio-ankle vascular index (CAVI) was developed as a novel BP-independent parameter of arterial stiffness. CAVI can be calculated from PWV at the origin of the aorta to the ankle portion of the tibial artery and from systolic and diastolic BPs measured at the upper brachial artery. CAVI reflects the overall stiffness of the aorta, femoral artery, and tibial artery. CAVI is superior to PWV as an index of arterial stiffness because it minimizes the effect on circulatory dynamics throughout the whole body and is less likely to be theoretically affected by BP. In fact, a study showed that CAVI weakly correlated with systolic blood pressure, whereas brachial-ankle pulse wave velocity strongly correlated with systolic and diastolic blood pressure in 482 hemodialysis patients. This theoretically BP-independent parameter of arterial stiffness is shown to be a useful tool to assess individuals who have BP variation at different times of the day and who suffer from white coat hypertension or are taking antihypertensive medications. We can ensure the validity of arterial stiffness measurements using this parameter. However, to the best of our knowledge, no studies have evaluated the association between arterial stiffness and executive function using CAVI till date.

The purpose of this study was to investigate the cross-sectional association between arterial stiffness measured by CAVI and executive function in community-dwelling elderly people.

**Methods**

**Participants**

We recruited elderly subjects from a community organization for elderly people at Kobe, Japan from August to September 2014. A total of 140 community-dwelling elderly people were enrolled in our study. An inclusion criterion was age ≥ 60 years. In the statistical analysis, subjects were excluded if they were < 60 years (n = 5) or answered that they had cerebral infarction (n = 5) or arteriosclerosis obliterans (n = 4) in a self-administered questionnaire. One hundred and twenty-six people met the inclusion criteria. Ethical approval for this study was given by the Ethics Committee of the Kobe University Graduate School of Health Sciences. All participants were properly informed about the study and signed written consent forms, in accordance with the Declaration of Helsinki, before participation.

**Measurements**

**Demographic Data and Global Cognition**

Height and weight were measured using standardized height and weight scales. Body mass index (BMI) was calculated in kg/m². A self-administered questionnaire was used to collect data on age, sex, history of past illnesses (Alzheimer’s disease, cerebral infarction, hypertension, hyperlipidemia, diabetes mellitus, cardiac disease, and pulmonary disease), antihypertensive medications, smoking history, and years of education. Global cognition was assessed using Mini Mental State Examination (MMSE) by a trained physical therapist or an occupational therapist.

**CAVI**

CAVI, systolic and diastolic BP (SBP and DBP), and heart rate (HR) were measured between both arms and ankles in a supine position using a VaSera-1000 (Fukuda Denshi Co. Ltd., Tokyo, Japan). CAVI was originally derived from the stiffness parameter β with application of Bramwell–Hill equation. The CAVI formula is provided below:

\[
\text{CAVI} = a/(2 \rho / \Delta P) \times \ln(P_s/P_d) \times \text{haPWV}^2 + b
\]

where \(P_s\) is systolic BP, \(P_d\) is diastolic BP, \(\rho\) is pulse wave velocity from the origin of the aorta to the tibial artery at the ankle through the femoral artery, \(\Delta P\) is \(P_s - P_d\), \(\rho\) is blood density, and \(a\) and \(b\) are con-
Executive Functions

Executive functions were assessed with one-to-one guidance by a trained physical therapist or an occupational therapist in a quiet room. The semantic fluency, phonemic fluency, and speed of processing were assessed as measures of executive function using the Category Word Fluency Test (CWFT), Letter Word Fluency Test (LWFT), and Digit Symbol Substitution Test (DSST), respectively. In CWFT, the participants were asked to list as many animals as possible within 1 min. The score was the number of different animals listed, with more number of animals listed indicating better function. In LWFT, the participants were instructed to say as many words as possible that begin with sound “Ka” within 1 min. The score was the number of different words listed, with more number of words listed indicating better function. In DSST, the participants were presented with nine symbols, each representing one of the nine (1–9) digits. A series of digits with a blank space for sketching the symbol underneath was presented on the same sheet of paper. Participants were asked to assign as many symbols as possible to the respective digits. The test length was 90 s, and the score was the number of correct number–symbol matches within that time frame, with higher score indicating better function.

Statistical Analysis

The sex differences of each variable were analyzed using the unpaired t-test or the Mann–Whitney test for age, body mass index, mean CAVI, SBP, DBP, HR, MMSE score, executive functions, and years of education and the χ² test for hypertension, hyperlipidemia, diabetes mellitus, cardiac disease, pulmonary disease, antihypertensive medication, and smoking history. Pearson or Spearman correlation analyses were performed to explore the association between executive function and each variable. In the multivariate analysis, a multiple linear regression analysis was performed to investigate whether arterial stiffness was independently associated with lower executive function, adjusting for demographic data, including age, sex, BMI, education, and other variables, such as MMSE, SBP, comorbidities, and life time smoking history. It has been reported that these factors were associated with arterial stiffness or cognitive decline. Statistical analysis was performed using STATA 13.1 (Stata Corp, College Station, TX, USA). A p value < 0.05 was considered statistically significant.

Results

The mean age of the study participants was 73.2 ± 6.1 years, and 85 (67.5%) of the participants were female. Table 1 shows the characteristics and executive functions of all subjects and the sex differences in each variable. The mean score and min–max ranges of executive functions were as follow: CWFT, 15.3 ± 4.7 (min–max: 4–29); LWFT, 11.9 ± 4.5 (4–28); and DSST, 44.7 ± 12.4 (14–75). Table 2 shows the correlations between executive functions and various parameters including executive function. In the univariate analysis, higher mean CAVI was correlated with lower CWFT (rho = −0.21, p = 0.02), LWFT (rho = −0.32, p < 0.001), and DSST (rho = −0.32, p < 0.001) (Table 2). In the multivariate analysis, higher mean CAVI was associated with lower LWFT (β = −0.21, p = 0.046), although there was no association with CWFT (β = −0.05, p = 0.611) and DSST (β = −0.06, p = 0.508). Older age is strongly associated with lower CWFT and DSST (CWFT; β = −0.25, p = 0.014 and DSST; β = −0.43, p < 0.001) (Table 3). Supplemental Table 1 shows the demographic data and executive functions according to the classification of age (60–64, 65–69, 70–74, 75–79, and >80 years). We performed a correlation analysis between mean CAVI and executive functions in each group. In the 70–74 years group, higher mean CAVI was correlated with lower LWFT (rho = −0.39, p = 0.006), and there was a tendency to have larger correlation coefficients in the association between mean CAVI and LWFT in the older groups (rho = −0.39, −0.22, and −0.30 in 70–74, 75–79, and >80 years groups, respectively) rather than younger groups (rho = 0.08 and 0.03 in 60–64 and 65–69 years groups, respectively) (Supplemental Table 2).

Discussion

We investigated the association between arterial stiffness measured according to CAVI and executive function in community-dwelling elderly people. Higher CAVI was associated with lower LWFT, whereas no association was observed with CWFT and DSST. Our results indicate a significant association between arterial stiffness and lower performance in phonemic fluency.

CAVI was developed with the objective of obtaining an arterial stiffness index that is theoretically not affected by BP at the time of measurement, unlike PWV. PWV is known to depend on the time of
Table 1. Sample Characteristics and sex differences

| Variable                  | All       | Male      | Female     | p value |
|---------------------------|-----------|-----------|------------|---------|
|                           | N=126     | N=41      | N=85       |         |
| Demographic data          |           |           |            |         |
| Age, years                | 73.2 ± 6.1| 73.4 ± 6.1| 73.1 ± 6.2| 0.785   |
| Body mass index, kg/m²    | 23.2 ± 2.9| 23.5 ± 3.0| 23.1 ± 2.9| 0.475   |
| Mean CAVI                 | 9.4 ± 1.2 | 9.6 ± 1.4 | 9.3 ± 1.1 | 0.264   |
| SBP, mmHg                 | 138.7 ± 18.3| 140.8 ± 19.3| 137.7 ± 17.8| 0.370   |
| DBP, mmHg                 | 82.7 ± 11.1| 84.4 ± 12.4| 81.9 ± 11.1| 0.247   |
| HR, beats/min             | 69.0 ± 12.4| 68.0 ± 14.8| 69.5 ± 11.2| 0.344   |
| MMSE, score               | 27.4 ± 1.9 | 27.5 ± 1.7 | 27.3 ± 2.0 | 0.579   |
| Executive function        |           |           |            |         |
| CWFT, count               | 15.3 ± 4.7 | 15.7 ± 4.5 | 15.1 ± 4.8 | 0.512   |
| LWFT, count               | 11.9 ± 4.5 | 11.9 ± 4.6 | 11.9 ± 4.5 | 0.952   |
| DSST, count               | 44.7 ± 12.4| 44.8 ± 12.7| 44.7 ± 12.3| 0.971   |
| Comorbidities             |           |           |            |         |
| Hypertension, %           | 53 (42.1)| 18 (43.9)| 35 (41.2)| 0.772   |
| Hyperlipidemia, %         | 26 (20.6)| 2 (4.9)| 24 (28.2)| 0.002** |
| Diabetes mellitus, %      | 8 (6.3)| 3 (7.3)| 5 (5.9)| 0.757   |
| Cardiac disease, %        | 13 (10.3)| 5 (12.2)| 8 (9.4)| 0.630   |
| Pulmonary disease, %      | 6 (4.8)| 4 (9.8)| 2 (2.4)| 0.068   |
| Antihypertensive medications, % | 45 (35.7) | 16 (39.0) | 29 (34.1) | 0.590   |
| Smoking history, %        | 33 (26.2)| 27 (65.9)| 6 (7.1)| <0.001** |
| Education, years          | 12.4 ± 2.2| 13.5 ± 2.4| 11.9 ± 2.0| <0.001** |

CAVI: cardio-ankle vascular index; Mean CAVI: the mean value of the right and left CAVI; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate; MMSE: Mini-Mental State Examination; CWFT: Category word fluency test; LWFT: Letter word fluency test; DSST: Digit symbol substitution test; Mean ± SD values are shown for age, Body mass index, Mean CAVI, SBP, DBP, HR, LWFT, CWFT, DSST, and education; % is shown for Comorbidities, Antihypertensive medications, and smoking history; *p<0.05; **p<0.01

Table 2. The bivariate analysis showing the correlations between executive functions and various parameters using Pearson or Spearman correlation

| Variable | CWFT | p value | LWFT | p value | DSST | p value |
|----------|------|---------|------|---------|------|---------|
| Age      | -0.32| 0.002** | -0.26| 0.003* | -0.51| <0.001**|
| BMI      | -0.07| 0.412   | -0.01| 0.879   | -0.06| 0.501   |
| Education| 0.12 | 0.188   | 0.21 | 0.017* | 0.32 | <0.001**|
| MMSE     | 0.29 | <0.001**| 0.17 | 0.057   | 0.19 | 0.029*  |
| Mean CAVI| -0.21| 0.020*  | -0.32| <0.001**| -0.32| <0.001**|
| SBP      | -0.07| 0.439   | -0.17| 0.061   | -0.10| 0.254   |
| DBP      | 0.05 | 0.545   | 0.13 | 0.158   | -0.13| 0.135   |
| HR       | 0.02 | 0.861   | -0.02| 0.819   | -0.02| 0.794   |
| Comorbidities | -0.04 | 0.621 | -0.14 | 0.111 | -0.00 | 0.987   |

Correlation coefficient: correlation coefficient determined according to the Pearson or Spearman correlation analysis, CWFT: Category word fluency test, LWFT: Letter word fluency test, DSST: Digit symbol substitution test, BMI: body mass index, MMSE: Mini-Mental State Examination, CAVI: cardio-ankle vascular index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate, Comorbidities: number of chronic diseases (hypertension, hyperlipidemia, diabetes mellitus, cardiac disease, and pulmonary disease), *p<0.05; **p<0.01; 1Spearman correlation coefficient
measurement and is unsuitable to evaluate individuals who are taking antihypertensive medications or suffering from masked hypertension or white coat hypertension. In addition, the use of antihypertensive medication has increased in elderly people. In our sample, 45 (35.7%) subjects were taking antihypertensive medications. We could ensure the validity of arterial stiffness measurements using CAVI, and we verified the association of arterial stiffness and executive function.

In the multivariate linear regression analysis in our study, CAVI was associated with lower LWFT, but not with lower CWFT and DSST after controlling the covariates. There are domain-specific differences in these executive functions. CWFT, also known as semantic fluency, requires a search through conceptual knowledge stores for semantic extensions derived from a target word. LWFT, also referred to as phonemic fluency, relies on lexical representation strategies\(^{18}\). Semantic and phonemic fluency are considered to be dependent on partially different neural circuits, with semantic fluency relying on temporal areas and phonemic fluency on more frontal regions\(^{19}\). DSST is a test of psychomotor performance, and it requires incidental memory, visuomotor coordination, and selective attention to filter irrelevant information\(^{20}\).

Moreover, there were age-related variances in these cognitive functions. Park et al. showed that the speed of processing measured using DSST strongly associated with aging. In contrast, semantic memory was relatively less affected by aging\(^{21}\). In our study, CWFT and DSST, particularly DSST, strongly associated with age, although LWFT had less association with age and was independently associated with mean CAVI after adjusting for age. When the subjects were divided by age, there also was a significant correlation between LWFT and mean CAVI in the 70–74 years group, and there was a tendency of having larger correlation coefficients in the older groups rather than younger groups (Supplemental Table 2). Our results indicated that arterial stiffness measured by CAVI domain specifically associated with phonemic fluency and that the magnitude of the association may be higher in older groups.

The mechanisms leading to the association between arterial stiffness and executive function is unclear. However, because CAVI is a marker of functional and structural changes in the arterial vessels, possible explanation can be proposed based on vessel wall pathology. Arterial stiffness has been found to be associated with structural changes in the brain, primarily white matter hyperintensities, cerebral lacunar infarction, and cortical brain atrophy\(^{22, 23}\). Regarding regional differences, cross-sectional and longitudinal studies showed that structural changes, such as white matter hyperintensities and lacunes, progressed with age, mainly in the frontal and parietal lobes\(^{24, 25}\). Increased arterial stiffness was also associated with increased lesions mainly in the frontal lobe\(^{26}\). These lesions in the frontal lobe have been independently associated with cognitive decline, particularly in the domains of executive function\(^{27, 28, 29}\). Further studies are needed to clarify the connections between arterial stiffness and regional differences in structural changes.

| Table 3. The associated factors of executive functions identified by multiple linear regression analyses |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| CWFT                                            | LWFT                                            | DSST                                            |
| Mean CAVI                                       | Mean CAVI                                       | Mean CAVI                                       |
| \(\beta\)                                       | \(p\) value                                     | \(\beta\)                                       | \(p\) value                                     | \(\beta\)                                       | \(p\) value                                     |
| Mean CAVI                                       | Mean CAVI                                       | Mean CAVI                                       | Mean CAVI                                       | Mean CAVI                                       | Mean CAVI                                       |
| Age                                             | -0.25                                           | -0.21                                           | -0.06                                           | 0.01                                            | 0.046*                                          | -0.43                                           | <0.001**                                        |
| sex                                             | -0.10                                           | 0.01                                            | 0.10                                            | 0.01                                            | 0.283                                           | 0.10                                            | 0.354                                           |
| BMI                                             | -0.07                                           | 0.10                                            | 0.01                                            | 0.01                                            | 0.895                                           | 0.01                                            | 0.895                                           |
| Education                                       | -0.01                                           | 0.20                                            | 0.25                                            | 0.25                                            | 0.038*                                          | 0.25                                            | 0.004**                                        |
| MMSE                                            | 0.31                                            | 0.12                                            | 0.14                                            | 0.14                                            | 0.190                                           | 0.14                                            | 0.086                                           |
| SBP                                             | 0.02                                            | 0.01                                            | 0.08                                            | 0.08                                            | 0.936                                           | 0.08                                            | 0.323                                           |
| Comorbidities                                   | 0.03                                            | -0.08                                           | 0.04                                            | 0.04                                            | 0.774                                           | 0.04                                            | 0.644                                           |
| Smoking history                                 | -0.06                                           | -0.09                                           | 0.04                                            | 0.04                                            | 0.569                                           | 0.04                                            | 0.716                                           |
| adjusted \(R^2\)                                | 0.14                                            | 0.11                                            | 0.29                                            | 0.001**                                        | 0.007**                                        | 0.001**                                        |

\(\beta\): Standardized regression coefficient, CWFT: Category word fluency test, LWFT: = Letter word fluency test, DSST: Digit symbol substitution test, CAVI: cardio-ankle vascular index, BMI: Body mass index, MMSE: Mini-Mental State Examination, SBP: Systolic blood pressure, Comorbidities: number of chronic diseases (hypertension, hyperlipidemia, diabetes mellitus, cardiac disease, and pulmonary disease) \(^*p<0.05, **p<0.01\)
in the brain and cognitive decline.

Arterial stiffness increases with age[11] and is associated with metabolic syndrome[30], diabetes mellitus[31], hypertension[32], and smoking[33]. Recent studies have shown that the CAVI value can be decreased by weight reduction[30], blood glucose control[34], hypertension control[35, 36], and smoking cessation[37]. In addition, moderate-to-vigorous intensity physical activities, such as brisk walking, jogging, aerobics, and other sports, are shown to attenuate arterial stiffening[37, 38]. Thus, in elderly people, improving lifestyle may prevent the decline of executive function through improving arterial stiffness. Further longitudinal studies are required to clarify the association of improvement of CAVI with executive function. These future studies may prove helpful in preventing the decline of executive function.

This study has several limitations. Because of the cross-sectional design of this study, the cause–effect relationship between CAVI and executive function is unclear. Moreover, we did not perform neuroimaging, which is more informative about structural changes in the brain. Finally, although we adjusted age, sex, BMI, education, MMSE, comorbidities, and smoking history, unmeasured variables, such as physical activity, could have affected the association between CAVI and executive function. Given these limitations, this is the first study to determine the association between arterial stiffness and executive function in community-dwelling elderly people using CAVI, which is a BP-independent parameter of arterial stiffness. Future research, including longitudinal and interventional studies, is necessary to confirm these results.

**Conclusion**

This is the first study to determine the association between CAVI and executive function in community-dwelling elderly people. Our study suggests that arterial stiffness measured according to CAVI associated with lower performance in phonemic fluency.

**References**

1. Clark LR, Schielser DM, Weissberger GH, Salomon DP, Delis DC, Bondi MW: Specific measures of executive function predict cognitive decline in older adults. J Int Neuropsychol Soc, 2012; 18: 118-127
2. Lezak, MD: In: Neuropsychological Assessment. 3. New York: Oxford University Press; 1995
3. Chen TY, Peronto CL, Edwards JD: Cognitive function as a prospective predictor of falls. J Gerontol B Psychol Sci Soc, 2012; 67: 720-728
4. Johnson JK, Lui LY, Yaffe K: Executive function, more than global cognition, predicts functional decline and mortality in elderly women. J Gerontol B Psychol Sci Med Sci, 2007; 62: 1134-1141
5. Schuur M, Henneman P, van Swieten JC, Zillikens MC, de Koning I, Janssens AC, Witteman JC, Aulchenko YS, Frants RR, Oostra BA, van Dijk KW, van Duikn CM: Insulin-resistance and metabolic syndrome are related to executive function in women in a large family-based study. Eur J Epidemiol, 2010; 25: 561-568
6. Watoson NL, Sutton-Tyrrell K, Rosano C, Boudreau RM, Hardy SE, Simonsick EM, Najjar SS, Laufer LJ, Yaffe K, Atkinson HH, Satterfield S, Newman AB: Arterial stiffness and cognitive decline in well-functioning older adults. J Gerontol A Biol Sci Med Sci, 2011; 66: 1336-1342
7. Zhong W, Cruickshanks KJ, Schubert CR, Carlson CM, Chappell RJ, Klein BE, Klein R, Acher CW: Pulse wave velocity and cognitive function in older adults. Alzheimer Dis Assoc Disord, 2014; 28: 44-49
8. Waldstein SR, Rice SC, Thayer JF, Najjar SS, Suteri A, Zonderman AB: Pulse pressure and pulse wave velocity are related to cognitive decline in the Baltimore longitudinal study of aging. Hypertension, 2007; 51: 99-104
9. Murakami S, Otsuka K, Miyashita Y, Saiki A, Takahashi M, Suzuki K, Takata M: Cardio-Ankle Vascular Index (CAVI) as novel indicator of arterial stiffness: theory, evidence, and perspectives. J Atheroscler Thromb, 2011; 18: 924-938
10. Shirai K, Utino J, Otsuka K, Takata M: A novel blood pressure-independent arterial wall stiffness parameter; cardio-ankle vascular index (CAVI). J Atheroscler Thromb, 2006; 13: 101-107
11. Takaki A, Ogawa H, Wakeyama T, Iwami T, Kimura M, Hadano Y, Matsuda S, Miyazaki Y, Hiratsuka A, Matsuzaki M: Cardio-ankle vascular index is superior to brachial-ankle pulse wave velocity as an index of arterial stiffness. Hypertens Res, 2008; 31: 1347-1355
12. Hayashi K, Handa H, Nagasawa S, Okumura A, Moritake K: Stiffness and elastic behavior of human intracranial and extracranial arteries. J Biomech, 1980; 13: 175-184

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**Conflicts of Interest**

None.
15) Kawasaki T, Sasayama S, Yagi S: Noninvasive assessment of the age related changes in stiffness of major branches of the human arteries. Cardiovascular Res, 1987; 21: 678-687

16) Branwell JC, Hill AV: Velocity of the pulse wave in man. Proc Roy Soc, 1922; 93B: 298-306

17) Shirai K, Utino J, Otsuka K, Takata M: A novel blood pressure-independent arterial stiffness: theory, evidence, and perspectives. J Atheroscler Thromb, 2006; 13: 101-107

18) Taler V, Phillips NA: Language performance in Alzheimer’s disease and mild cognitive impairment: a comparative review. J Clin Exp Neuropsychol, 2008; 30: 501-556

19) Henry JD, Crawford JR: A meta-analytic review of verbal fluency performance following focal cortical lesions. Neuropsychology, 2004; 18: 284-295

20) Wechsler D: Wechsler Adult Intelligence Scale–Revised Manual. Psychological Corporation, New York, 1981

21) Park DC, Smith AD, Lautenschlager G, Earles JL, Fieske D, Zwahr M, Gaines CL: Mediators of long-term memory performance across the life span. Psychology and Aging, 1996; 11: 621-637

22) Saji N, Shimizu H, Kawarai T, Tadano M, Kita Y, Yokono K: Increased brachial-ankle pulse wave velocity is independently associated with white matter hyperintensities. Neuroepidemiology, 2011; 36: 252-257

23) Saji N, Kimura K, Shimizu H, Kita Y: Association between silent brain infarct and arterial stiffness indicated by brachial-ankle pulse wave velocity. Intern Med, 2012; 51: 1003-1008

24) Ogama N, Yoshida M, Nakai T, Niida S, Yoba K, Sakurai T: Frontal white matter hyperintensity predicts lower urinary tract dysfunction in older adults with amnestic mild cognitive impairment and Alzheimer’s disease. Geriatr Gerontol Int, 2015, in press

25) Gouw AA, van der Flier WM, Fazekas F, v, Pantoni L, Poggesi A, Inzitari D, Erkinjuntti T, Wahlund LO, Waldemar G, Schmidt R, Scheltens P, Barkhof F; LADIS Study Group: Progression of white matter hyperintensities and incidence of new lacunes over a 3-year period: the Leukoaraiosis and Disability study, Stroke, 2008; 39: 1414-1420

26) Rosano C, Watson N, Chang Y, Newman AB, Aizenstein HJ, Du Y, Venkatraman V, Harris TB, Barinas-Mitchell E, Sutton-Tyrrell K: Aortic pulse wave velocity predicts focal white matter hyperintensities in a biracial cohort of older adults. Hypertension, 2013; 61: 160-165

27) Gunning-Dixon FM, Raz N: The cognitive correlates of white matter abnormalities in normal aging: a quantitative review. Neuropsychology, 2000; 14: 224-232

28) Herrmann MJ, Ehls AC, Fallgatter AJ: Frontal activation during a verbal-fluency task as measured by near-infrared spectroscopy. Brain Res Bull, 2003; 61: 51-56

29) Sasson E, Doniger GM, Pastemak O, Tarrsch R, Assaf Y: Structural correlates of cognitive domains in normal aging with diffusion tensor imaging. Brain Struct Funct, 2012; 217: 503-515

30) Satoh N, Shimatsu A, Kotani K, Himeno A, Majima T, Yamada K, Suganami T, Ogawa Y: Highly purified eicosapentaenoic acid reduces cardio-ankle vascular index in association with decreased serum amyloid A-LDL in metabolic syndrome. Hypertens Res, 2009; 32: 1004-1008

31) Ibata J, Sasaki H, Kakimoto T, Matsuno S, Nakatani M, Kobayashi M, Tatsumi K, Nakano Y, Wakasagi H, Furuta H, Nishi M, Nanjo K: Cardio-ankle vascular index measures arterial wall stiffness independent of blood pressure. Diabetes Res Clin Pr, 2008; 80: 265-270

32) Kubozono T, Miyata M, Ueyama K, Nagaki A, Otsuji Y, Kusano K, Kubozono O, Tazawa C: Clinical significance and reproducibility of new arterial distensibility index. Circ J, 2007; 71: 89-94

33) Noike H, Nakamura K, Sugiyama Y, Iizuka T, Shimizu K, Takahashi M, Hirano K, Suzuki M, Mikamo H, Nakanishi T, Shirai K: Changes in cardio-ankle vascular index in smoking cessation. J Atheroscler Thromb, 2009; 16: 568-575

34) Nagayama D, Saiki A, Endo K, Yamaguchi T, Ban N, Kawana H, Ohira M, Oyama T, Miyashita Y, Shirai K: Improvement of cardio-ankle vascular index by glimepiride in type 2 diabetic patients. Int J Clin Pract, 2010; 64: 1796-1801

35) Uehara G, Takeda H: Relative effects of telmisartan, candesartan and losartan on alleviating arterial stiffness in patients with hypertension complicated by diabetes mellitus: an evaluation using the cardio-ankle vascular index (CAVI). J Int Med Res, 2008; 36: 1094-1102

36) Sasaki H, Saiki A, Endo K, Yamaguchi T, Ban N, Kawana H, Ohira M, Oyama T, Miyashita Y, Shirai K: Protective effects of efonidipine, a T- and L-type calcium channel blocker, on renal function and arterial stiffness in type 2 diabetic patients with hypertension and nephropathy. J Atheroscler Thromb, 2009; 16: 568-575

37) Seals DR, Walker AE, Pierce GL, Lesniewski LA: Habitual exercise and vascular aging. J Physiol, 2009; 587: 5541-5549

38) Sugawara J, Otsuki T, Tanabe T, Hayashi K, Maeda S, Matsuda M: Physical activity duration, intensity, and arterial stiffening in postmenopausal women. Am J Hypertens, 2006; 19: 1032-1103
## Supplemental Table 1. The differences in demographic data and executive function between the age groups

| Variable                      | Age 60–64 | Age 65–69 | Age 70–74 | Age 75–79 | Age 80–90 | p value |
|-------------------------------|-----------|-----------|-----------|-----------|-----------|---------|
|                               | N = 13    | N = 18    | N = 50    | N = 26    | N = 19    |         |
| **Demographic data**          |           |           |           |           |           |         |
| Age, years                    | 62.2 ± 1.4| 67.9 ± 1.4| 72.3 ± 1.3| 76.9 ± 1.5| 82.9 ± 3.2| <0.001**|
| Body mass index, kg/m²        | 22.4 ± 3.2| 22.4 ± 2.9| 23.8 ± 2.8| 22.3 ± 3.1| 24.4 ± 1.8| 0.030*  |
| Education, years              | 14.2 ± 2.3| 12.4 ± 2.0| 12.2 ± 2.0| 12.3 ± 2.1| 11.9 ± 3.0| 0.041*  |
| Mean CAVI                     | 8.3 ± 0.8 | 8.9 ± 1.0 | 9.4 ± 1.0 | 10.0 ± 1.1| 10.1 ± 1.2| <0.001**|
| SBP, mmHg                     | 123.1 ± 14.4| 139.2 ± 20.0| 139.7 ± 17.0| 141.0 ± 17.6| 143.3 ± 19.7| 0.022*  |
| DBP†, mmHg                    | 77.5 ± 8.4 | 85.6 ± 15.7| 82.8 ± 9.8 | 83.8 ± 10.3| 81.8 ± 12.0| 0.531   |
| HR †, beats/min               | 69.1 ± 8.5 | 69.7 ± 10.5| 65.3 ± 11.3| 75.2 ± 16.0| 69.7 ± 11.1| 0.034*  |
| MMSE, score                   | 28.2 ± 1.6 | 28.2 ± 1.6| 27.3 ± 2.1 | 26.6 ± 2.0 | 27.3 ± 1.7 | 0.038*  |
| **Executive function**        |           |           |           |           |           |         |
| CWFT, count                   | 18.3 ± 5.3 | 17.9 ± 4.3| 15.2 ± 4.1| 13.7 ± 3.7| 13.1 ± 5.4| <0.001**|
| LWFT‡, count                  | 15.4 ± 5.3 | 12.9 ± 4.3| 11.6 ± 3.8| 11.2 ± 5.6| 10.1 ± 2.7| 0.027*  |
| DSST, count                   | 59.1 ± 12.2| 49.6 ± 11.4| 45.0 ± 11.4| 38.6 ± 9.8| 38.2 ± 9.3| <0.001**|

* p value was calculated using an one-way analysis of variance or Kruskal–Wallis rank test. CAVI: cardio-ankle vascular index, Mean CAVI: the mean value of the right and left CAVI, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate, MMSE: Mini-mental state examination, CWFT: Category word fluency test, LWFT: Letter word fluency test, DSST: Digit symbol substitution test, Mean ± SD values are shown age, Body mass index, Mean CAVI, SBP, DBP, HR, LWFT, CWFT, DSST and education, † p value was calculated using Kruskal–Wallis rank test, * p < 0.05, ** p < 0.01

## Supplemental Table 2. The bivariate analysis showing the correlations between mean CAVI and executive functions using spearman correlation

| Variable | Age 60–64 | Age 65–69 | Age 70–74 | Age 75–79 | Age 80–90 | P value |
|----------|-----------|-----------|-----------|-----------|-----------|---------|
|          | N = 13    | N = 18    | N = 50    | N = 26    | N = 19    |         |
| MMSE     | 0.23      | 0.458     | -0.07     | 0.794     | 0.06      | 0.69    | 0.10    | 0.627   | 0         | 9.84    |
| CWFT     | 0.15      | 0.633     | 0.08      | 0.74      | -0.24     | 0.098   | 0.05    | 0.826   | 0.12      | 0.611   |
| LWFT     | 0.08      | 0.788     | 0.03      | 0.893     | -0.39     | 0.006** | -0.22   | 0.29    | -0.30     | 0.22    |
| DSST     | 0.55      | 0.051     | -0.12     | 0.639     | -0.24     | 0.1     | -0.07   | 0.737   | -0.09     | 0.708   |

* rho: Spearman correlation coefficient, MMSE: Mini-Mental State Examination, CWFT: Category word fluency test, LWFT: Letter word fluency test, DSST: Digit symbol substitution test, * p < 0.05 ** p < 0.01