Journal of the American Heart Association

ORIGINAL RESEARCH

Association of Arterial Stiffness and Atherosclerotic Burden With Brain Structural Changes Among Japanese Men

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BACKGROUND: Little is known regarding whether arterial stiffness and atherosclerotic burden are each independently associated with brain structural changes. Simultaneous assessments of both arterial stiffness and atherosclerotic burden in associations with brain could provide insights into the mechanisms of brain structural changes.

METHODS AND RESULTS: Using data from the SESSA (Shiga Epidemiological Study of Subclinical Atherosclerosis), we analyzed data among 686 Japanese men (mean [SD] age, 67.9 [8.4] years; range, 46–83 years) free from history of stroke and myocardial infarction. Brachial-ankle pulse wave velocity and coronary artery calcification on computed tomography scans were measured between March 2010 and August 2014. Brain volumes (total brain volume, gray matter, Alzheimer disease signature and prefrontal) and brain vascular damage (white matter hyperintensities) were quantified using brain magnetic resonance imaging from January 2012 through February 2015. In multivariable adjustment models including mean arterial pressure, when brachial-ankle pulse wave velocity and coronary artery calcification were entered into the same models, the β (95% CI) for Alzheimer disease signature volume for each 1-SD increase in brachial-ankle pulse wave velocity was −0.33 (−0.64 to −0.02), and the unstandardized β (95% CI) for white matter hyperintensities for each 1-unit increase in coronary artery calcification was 0.68 (0.05–1.32). Brachial-ankle pulse wave velocity and coronary artery calcification were not statistically significantly associated with total brain and gray matter volumes.

CONCLUSIONS: Among Japanese men, higher arterial stiffness was associated with lower Alzheimer disease signature volumes, whereas higher atherosclerotic burden was associated with brain vascular damage. Arterial stiffness and atherosclerotic burden may be independently associated with brain structural changes via different pathways.

Key Words: Alzheimer disease ■ arterial stiffness ■ atherosclerosis ■ brain vascular damage ■ brain volume ■ coronary artery calcification

Arterial stiffness is defined as the decline in the ability of an artery to expand and contract in response to blood pressure changes.[1] Greater arterial stiffness reflects an increase in the structural and functional stiffness of arteries.[2] This phenomenon occurs due to the stiffening and thickening of the arterial wall that is mainly caused by aging and hypertension.[3] Stiffening of the arteries, assessed using pulse wave velocity (PWV), may contribute to microvascular brain injury by exposing the cerebral vasculature to

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This manuscript was sent to Jose Gutierrez, MD, MPH, Guest Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.028586

For Sources of Funding and Disclosures, see page 8.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- This population-based observational study of Japanese men demonstrated that higher brachial-ankle pulse wave velocity was associated with lower volumes of Alzheimer disease signature, and higher coronary artery calcification score was associated with greater white matter hyperintensities.
- Higher arterial stiffness was associated with lower brain volumes related to cognition, and higher coronary artery calcification score was associated with brain vascular damage.

What Are the Clinical Implications?

- The present study suggests that arterial stiffness and atherosclerotic burden may contribute to cognitive decline through mechanisms of brain atrophy and brain vascular damage.
- Findings from this study emphasize the importance of preventing and delaying the progression of arterial stiffness and atherosclerotic burden to reduce the public health burden of cardiovascular disease.

Nonstandard Abbreviations and Acronyms

ARIC	Atherosclerosis Risk in Communities
baPWV	brachial-ankle pulse wave velocity
cfPWV	carotid-femoral pulse wave velocity
PWV	pulse wave velocity
SESSA	Shiga Epidemiological Study of Subclinical Atherosclerosis
TCBV	total cerebral brain volume
TIV	total intracranial volume
WMHs	white matter hyperintensities

high pressure and pulsatility.[4] Indeed, greater arterial stiffness has been shown to be associated with subclinical vascular brain injury (ie, white matter hyperintensities [WMHs]), smaller total brain volume, and Alzheimer disease (AD) signature volume (ie, entorhinal cortex, hippocampus, parahippocampal, precuneus, cuneus, and inferior parietal lobules).[5–7]

Atherosclerotic burden, assessed using coronary artery calcification (CAC) on computed tomography (CT), reflects accumulation of lipids, inflammatory cells, and fibrous elements.[1] Atherosclerotic burden is caused by dyslipidemia and diabetes.[8] Higher CAC has been shown to be associated with reduced white matter, gray matter, and total brain volumes,[9] and greater white matter injury.[10] However, no studies in a community-based population have assessed whether arterial stiffness is associated with brain structural changes independently of atherosclerotic burden, and whether atherosclerotic burden is associated with brain structural changes independently of arterial stiffness. Available evidence on the association of arterial stiffness or atherosclerotic burden with brain structural changes is mostly reported from Western populations, patients with cardiovascular disease (CVD),[5] and older adults.[9] Little is known regarding independent associations of arterial stiffness and atherosclerotic burden with brain structural changes in an Asian community-based population. Elucidating these associations is important since Asian populations have higher death and morbidity from stroke[11] and increasing trends in dementia prevalence compared with Western populations.[12] Simultaneous assessments of both arterial stiffness and atherosclerotic burden in investigations of associations with brain structural changes could clarify the mechanisms of brain aging, which may lead to the identification of a target for maintaining brain health.

Using a database from SESSA (Shiga Epidemiological Study of Subclinical Atherosclerosis), we assessed whether brachial-ankle PWV (baPWV) and CAC are each independently associated with brain volumes among individuals without a history of CVD. We also assessed the independent association of baPWV and CAC with brain vascular damage among Japanese men.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Participants and Design

SESSA is an observational study that investigates factors associated with subclinical atherosclerosis in a community-dwelling population. This study was first funded by the Japanese government to conduct examinations for men in 2006 to 2015, and for women in 2015 to 2022. For the SESSA men's study, baseline data collection was conducted between 2006 and 2008. For the SESSA women's study, data collection began in 2015 and is ongoing. The difference in the data collection periods for men and women is due to the fact that the research budget was not enough to include both at the same time. In the current study, we used only data from the SESSA men's study. Details of the SESSA men's study have been reported previously.[13–15] In brief, 2379 Japanese men aged 40 to 79 years were randomly invited on the basis of the residents' registry of Kusatsu City, Shiga Prefecture, Japan. Of the 2379 invitees, 1094 healthy men agreed to participate and completed a baseline examination

between 2006 and 2008. Subsequently, 853 attended the follow-up examination between 2010 and 2014 and were recruited for brain magnetic resonance imaging (MRI) examination. Of the 853 participants, 740 underwent 1.5T MRI examination between 2012 and 2015. Of the 740 participants, we excluded 54 with a history of stroke, history of myocardial infarction, and/or missing baPWV measurements, leaving 686 participants for the final analysis (Figure S1).

All participants provided written informed consent. This study was approved by the Institutional Review Board of Shiga University of Medical Science (G2008-61) and followed the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Brachial-Ankle PWV

baPWV measured between 2010 and 2014 was used for the current analysis. An automatic waveform analyzer (Form I PWV/ABI; Omron Health Care Co. Ltd, Kyoto, Japan) was used for baPWV measurement.[16] The measurement was completed with participants in the supine position after 5 minutes of rest. The average of left and right baPWV values was used in the analysis. Higher values of baPWV indicate higher levels of arterial stiffness.

Coronary Artery Calcification

CT images obtained between 2010 and 2014 were used for the current analysis. The images were acquired using electron-beam CT from a C-150 scanner (GE Imatron, South San Francisco, CA) or using 16-channel multidetector row CT from an Aquilion scanner (Toshiba, Tokyo, Japan). CAC scores were calculated using the Agatston method.[17] A physician trained in CT reading at the Cardiovascular Institute of the University of Pittsburgh, who was blinded to the clinical information of the participants, read all the CT images and calculated the CAC scores.[15,16]

Brain MRI Acquisition

Brain MRI was performed using a 1.5-Tesla MRI scanner (Signa HDxt 1.5T, version 16; GE Healthcare, Milwaukee, WI) at Shiga University of Medical Science Hospital between 2012 and 2015, ≈2 years after baPWV and CAC data collection. The high-resolution MRI scans obtained 3-dimensional, T1-weighted, spoiled gradient recalled acquisition images (repetition time=13.5 ms, echo time=5.8 ms, thickness=1.6/–0.8 mm, fractional anisotropy=15°, frequency encoding=288, 256×256 matrix). All MRI images were analyzed using Brain Anatomical Analysis Using Diffeomorphic Deformation version 4.4 software.[18] We also used the automated voxel-based morphometry toolbox in Statistical Parametric Mapping version 12 software with extensions such as Computational Anatomy Toolbox 12 software to obtain the brain volumes and regions of interest on a voxel-by-voxel basis. Two neurosurgeons (K.N. and A.S.) certified by the Japan Neurosurgery Society independently reviewed the MRI images. They were blinded to participants' clinical information during the evaluation of images. Gray matter and white matter volumes were measured separately in milliliters and were added together to obtain the total cerebral brain volume (TCBV). Total intracranial volume (TIV) was quantified during automatic segmentation. We also quantified brain volumes for priori selected cognition-related regions of interest, including prefrontal and AD signature volume. AD signature volume included the entorhinal cortex; hippocampus;and parahippocampal, precuneus, cuneus, and inferior parietal lobules.[6] The volume of WMHs was measured for the assessment of brain vascular damage. Detailed brain MRI procedures have been described elsewhere.[19,20]

Assessment of Covariates

Sociodemographic characteristics and lifestyle factors, including age, total years of education, smoking status, alcohol consumption, medical history, and use of medication, were collected using a self-administered questionnaire when baPWV and CAC measurements were obtained. Blood pressures were measured on the right arm while seated using an automated sphygmomanometer (BP-8800; Omron Health Care Co., Ltd., Tokyo, Japan). Blood pressure was measured twice after participants were at rest for 5 minutes, and the average was recorded. Hypertension was diagnosed as having systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg and/or use of antihypertensive medication. Blood samples were collected from participants after 12-hour fast for glycated hemoglobin (HbA_{1c}) concentrations, fasting blood glucose, and serum lipid concentration. Diabetes was diagnosed as fasting blood glucose ≥6.99 mmol/L (≥126 mg/dL), or HbA_{1c} ≥6.5% (National Glycohemoglobin Standardization Program) or use of antidiabetic medications. Dyslipidemia was diagnosed as having low-density lipoprotein cholesterol ≥3.6 mmol/L (140 mg/dL) or high-density lipoprotein (HDL) cholesterol <1.0 mmol/L (40 mg/dL) or use of lipid-lowering medication. Detailed methods are described in Data S1.

Statistical Analysis

Descriptive statistics were used to characterize participants' demographics and clinical characteristics. Continuous variables were presented using means (SD) for normally distributed data or medians (interquartile range) for skewed data. Frequencies and percentages were reported for categorical variables. Multivariable linear regression analyses were used to determine associations between arterial stiffness and brain structural changes. We log-transformed the extent of WMHs due

to skewness. For CAC analysis, we log-transformed the CAC value (log [CAC+1]) since the proportion of participants with CAC >0 is high and there was a positive skew of values among those with CAC >0.[21] We repeated the multivariable linear regression analysis for the association between log CAC and brain structural changes. β coefficients and corresponding 95% CIs were computed for 1-SD increments in baPWV, and unstandardized βs were computed for 1-unit increases in log CAC. We also reported the unstandardized β for the association between arterial stiffness and brain structural changes as supplementary analyses.

Model 1 is unadjusted. In model 2, we adjusted for age (in years) and TIV. For CAC analyses, we additionally adjusted for CT type since 2 methods were used for CAC measurements. In model 3, we additionally adjusted for smoking, alcohol drinking status, total years of education, HbA_{1c}, non-HDL cholesterol, mean arterial pressure (MAP), diabetes medication use, dyslipidemia medication use, and hypertension medication use (the last 3 were included in the model as separate covariates). In model 4, both baPWV and CAC were simultaneously assessed in the same model, adjusted for all covariates that were included in model 3.

We performed 4 sensitivity analyses. First, we analyzed the associations between arterial stiffness and subregions of AD signature volumes. Second, we excluded participants taking antihypertensive medication because it could affect both baPWV and brain measures[22,23] and may attenuate or exaggerate the association of baPWV with brain measures. These confounding effects may have remained even though we adjusted for antihypertensive medication use in models 3 and 4 described above. Third, we analyzed the association between CAC and brain structural changes using 2 CAC categories (CAC=0 and CAC >0). Fourth, we adjusted for antihypertensive medication use instead of the diagnosis of hypertension. As a prespecified analysis plan, all analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC) and a 2-sided significance level of <0.05. We did not adjust for multiple testing since our analyses were not hypothesis free; that is, this study was executed on the basis of prior studies that illustrated the associations of arterial stiffness and atherosclerotic burden with brain structural changes.[6,7,24]

RESULTS

The final analytical sample comprised 686 participants (age [mean±SD], 67.9±8.4 years, range, 46–83 years), of whom 135 (19.7%) were current smokers, 560 (81.6%) were current drinkers, and 256 (37.3%) were using antihypertensive medication (Table 1). Of the 686 participants, 55.1% had hypertension, 56.6% had dyslipidemia, and 20.9% had diabetes. The mean±SD for baPWV was 1728.5±353.6 cm/s and median (interquartile range) for CAC score was 26.3 (166.5). The distribution of baPWV is illustrated in Figure S2. The distribution of participants' ages, hypertension status, and systolic and diastolic blood pressure with baPWV is presented in Figure S3.

Table 1. Demographic and Clinical Characteristics of 686 Men Aged 46 to 83 Years in SESSA Study (2010–2014), Shiga, Japan

Clinical characteristics	SESSA participants (n=686)
Age, y, mean±SD	67.9±8.4
Education, y, mean±SD	12.0±4.0
Current smoker, n (%)	135 (19.7)
Current drinker, n (%)	560 (81.6)
BMI, kg/m^2, mean±SD	23.3±2.9
SBP, mm Hg, mean±SD	131.8±16.8
DBP, mm Hg, mean±SD	77.2±10.5
MAP, mm Hg, mean±SD	95.4±11.5
Heart rate, bpm, mean±SD	64.6±10.5
Total cholesterol, mg/dL, mean±SD	202.8±34.0
Triglycerides, mg/dL, median (IQR)	101.0 (70.0)
HDL-C, mg/dL, mean±SD	59.5±16.5
LDL-C, mg/dL, mean±SD	118.9±31.9
Non-HDL-C, mg/dL, mean±SD	143.3±32.6
HbA_{1c} NGSP, %, mean±SD	5.91±0.8
Antihypertensive medication, n (%)	256 (37.3)
Antidiabetic medication, n (%)	102 (14.9)
Medication for dyslipidemia, n (%)	141 (20.6)
Hypertension, n (%)	378 (55.1)
Diabetes, n (%)	143 (20.9)
Dyslipidemia, n (%)	388 (56.6)
baPWV, cm/s, mean±SD	1728.5±353.6
CAC score, median (IQR)	26.3 (166.5)

All values are presented as mean±SD for continuous variables except for triglycerides and CAC score, median (IQR). Frequency and percentages are presented for categorical variables.

baPWV indicates brachial-ankle pulse wave velocity; BMI, body mass index; bpm, beats per minute; CAC, coronary artery calcification; DBP, diastolic blood pressure; HbA_{1c} NGSP, glycated hemoglobin according to the National Glycohemoglobin Standardization Program; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MAP, mean arterial pressure; SBP, systolic blood pressure; and SESSA, Shiga Epidemiological Study of Subclinical Atherosclerosis.

Table 2 shows the association of arterial stiffness with brain volumes and brain vascular damage. In unadjusted models, higher baPWV was significantly associated with low TCBV (β=−29.12 for 1-SD increment in baPWV [95% CI, −36.16 to −22.07]; P<0.001), gray matter (β=−15.43 for 1-SD increment in baPWV [95% CI, −19.04 to −11.82]; P<0.001), AD signature (β=−1.58 for 1-SD increment in baPWV [95% CI, −1.96 to −1.21]; P<0.001), prefrontal (β=−2.89 for 1-SD increment in baPWV [95% CI, −3.63 to −2.15]; P<0.001), and hippocampus

Table 2. The Association Between Arterial Stiffness and Brain Structural Changes for 1-SD Increment in baPWV in Men of SESSA Study (2010–2014, n=686)

Arterial stiffness	Brain volume					Brain vascular damage
	Total cerebral brain volume β (95% CI)	Gray matter volume β (95% CI)	AD signature volume β (95% CI)	Prefrontal volume β (95% CI)	Hippocampus volume β (95% CI)	Log white matter hyperintensities β (95% CI)
Model 1	−29.12 (−36.16 to −22.07)*	−15.43 (−19.04 to −11.82)*	−1.58 (−1.96 to −1.21)*	−2.89 (−3.63 to −2.15)*	−0.40 (−0.47 to −0.32)*	0.25 (0.21 to 0.29)*
Model 2	−2.89 (−6.64 to 0.86)	−2.21 (−4.44 to 0.03)	−0.27 (−0.54 to −0.01)*	−0.66 (−1.17 to −0.15)*	−0.08 (−0.15 to −0.02)*	0.08 (0.05 to 0.12)*
Model 3	−1.82 (−6.19 to 2.56)	−1.47 (−4.05 to 1.11)	−0.35 (−0.66 to −0.04)*	−0.32 (−0.90 to 0.27)	−0.08 (−0.15 to −0.002)*	0.04 (0.001 to 0.08)*
Model 4	−1.56 (−5.93 to 2.80)	−1.35 (−3.93 to 1.24)	−0.33 (−0.64 to −0.02)*	−0.29 (−0.88 to 0.30)	−0.07 (−0.15 to 0.002)	0.04 (−0.004 to 0.07)

Data are displayed as standardized βs (β and 95% CI) after fitting linear regression. The 1-SD of baPWV was equivalent to 353.6 cm/s. Model 1 was unadjusted. Model 2 includes adjustment for age and TIV. Model 3 includes adjustment for age; TIV; smoking; drinking status; total years of education; HbA_{1c}; non-HDL cholesterol; MAP; and medication status for diabetes, hypertension, and dyslipidemia. Model 4 was inclusion of both baPWV and CAC simultaneously in the same model, adjusted for all covariates that were included in Model 3.

AD indicates Alzheimer disease; baPWV, brachial-ankle pulse wave velocity; CAC, coronary artery calcification; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; MAP, mean arterial pressure; SESSA, Shiga Epidemiological Study of Subclinical Atherosclerosis; and TIV, total intracranial volume.

*P<0.05.

volumes (β=−0.40 for 1-SD increment in baPWV [95% CI, −0.47 to −0.32]; P<0.001); and with greater log WMHs (β=0.25 for 1-SD increment in baPWV [95% CI, 0.21–0.29]; P<0.001). However, in model 3 (that adjusted for age; TIV; smoking status; drinking status; educational levels; HbA_{1c}; non-HDL cholesterol; MAP; and medication status for hypertension, diabetes, and dyslipidemia), higher baPWV was associated with lower AD signature (β=−0.35 for 1-SD increment in baPWV [95% CI, −0.66 to −0.04]; P=0.027), hippocampus volumes (β=−0.08 for 1-SD increment in baPWV [95% CI, −0.15 to −0.002]; P=0.044) and log WMHs (β=0.04 for 1-SD increment in baPWV [95% CI, 0.001–0.08]; P=0.043). When both baPWV and CAC were entered into the same model, higher baPWV was significantly associated with lower AD signature volume (β=−0.33 for 1-SD increment in baPWV [95% CI, −0.64 to −0.02]; P=0.037). We further performed an analysis on the association between baPWV and subregions of AD signature volume (Table S1). Higher baPWV was associated with lower parahippocampal volume (β=−0.06 for 1-SD increment in baPWV [95% CI, −0.11 to −0.004]; P=0.037). In 430 participants not taking antihypertensive medications, no significant associations were observed between baPWV with TCBV or gray matter, AD signature, prefrontal, or hippocampus volumes in all models (Table S2). baPWV was significantly associated with log WMHs (β=0.06 for 1-SD increment in baPWV [95% CI, 0.003–0.11]; P=0.037) after adjustment for age; TIV; smoking status; drinking status; educational levels; HbA_{1c}; non-HDL cholesterol; MAP; and medication status for diabetes, hypertension, and dyslipidemia. However, the association was attenuated after further adjustment for CAC.

Table 3 shows the association of CAC with brain volumes and brain vascular damage. In unadjusted models, higher CAC was significantly associated with lower TCBV (unstandardized β=−17.06 for 1 – unit of log CAC [95% CI, −23.56 to −10.55]; P<0.001), lower gray matter (unstandardized β=−8.97 for 1 – unit of log CAC [95% CI, −12.30 to −5.63]; P<0.001), AD signature (unstandardized β=−0.89 for 1 – unit of log CAC [95% CI, −1.24 to −0.55]; P<0.001), prefrontal (unstandardized β=−1.63 for 1 – unit of log CAC [95% CI, −2.31 to −0.94]; P<0.001) and hippocampus volumes (unstandardized β=−0.21 for 1 – unit of log CAC [95% CI, −0.29 to −0.14]; P<0.001); and with greater WMHs (unstandardized β=2.18 for 1 – unit of log CAC [95% CI, 1.51–2.85]; P<0.001). However, in model 3 (that adjusted for age; TIV; CT type; smoking status; drinking status; educational levels; HbA_{1c}; non-HDL cholesterol; MAP; and medication status for hypertension, diabetes, and dyslipidemia), higher CAC was associated with greater WMHs (unstandardized β=0.71 for 1 – unit of log CAC [95% CI, 0.08–1.35]; P=0.028). When both

Table 3. Multivariable Linear Regression of the Association Between Log CAC With Brain Structural Changes for 1 – Unit of Log CAC in Men of SESSA Study (2010–2014, n=686)

Log CAC	Brain volume (mL)					Brain vascular damage
	Total cerebral brain volume B (95% CI)	Gray matter volume B (95% CI)	AD signature volume B (95% CI)	Prefrontal volume B (95% CI)	Hippocampus volume B (95% CI)	White matter hyperintensities B (95% CI)
Model 1	−17.06 (−23.56 to −10.55)*	−8.97 (−12.30 to −5.63)*	−0.89 (−1.24 to −0.55)*	−1.63 (−2.31 to −0.94)*	−0.21 (−0.29 to −0.14)*	2.18 (1.51 to 2.85)*
Model 2	−2.92 (−6.03 to 0.20)	−1.71 (−3.58 to 0.16)	−0.17 (−0.39 to 0.05)	−0.39 (−0.82 to 0.03)	−0.03 (−0.09 to 0.02)	1.07 (0.45 to 1.68)*
Model 3	−2.20 (−5.45 to 1.04)	−1.12 (−3.04 to 0.80)	−0.19 (−0.42 to 0.04)	−0.21 (−0.65 to 0.23)	−0.03 (−0.09 to 0.02)	0.71 (0.08 to 1.35)*
Model 4	−2.09 (−5.35 to 1.17)	−1.02 (−2.95 to 0.91)	−0.17 (−0.40 to 0.07)	−0.19 (−0.63 to 0.25)	−0.03 (−0.08 to 0.03)	0.68 (0.05 to 1.32)*

Data are displayed as unstandardized βs (95% confidence interval). CAC was transformed as log (CAC+1). Model 1 was unadjusted. Model 2 includes adjustment for age, TIV, and CT type. Model 3 includes adjustment for age; TIV; CT type; smoking; drinking status; total years of education; HbA_{1c}; non-HDL cholesterol; MAP; and medication status for diabetes, hypertension, and dyslipidemia. Model 4 was inclusion of both baPWV and CAC simultaneously in the same model, adjusted for all covariates that were included in Model 3.

AD indicates Alzheimer disease; baPWV, brachial-ankle pulse wave velocity; CAC, coronary artery calcification; CT, computed tomography; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; MAP, mean arterial pressure; SESSA, Shiga Epidemiological Study of Subclinical Atherosclerosis; and TIV, total intracranial volume.

*P<0.05.

CAC and baPWV were entered into the same model, higher CAC was significantly associated with greater WMHs (unstandardized β=0.68 for 1 – unit of log CAC [95% CI, 0.05 to 1.32]; P=0.035). In 430 participants not taking antihypertensive medications, higher CAC was significantly associated with greater WMHs in all adjusted models. When both CAC and baPWV were entered into the same model, higher CAC was also significantly associated with greater WMHs among participants not taking antihypertensive medications (unstandardized β=0.97 for 1 – unit of log CAC [95% CI, 0.23–1.70]; P=0.010).

Of the 686 participants, two-thirds (66.8%) had a CAC score >0. We performed the analysis for the association between CAC >0 and brain structural changes (Table S3). Compared with participants with CAC=0, those with CAC >0 had higher WMHs in model 1 (unstandardized β=1.80 [95% CI, 0.36–3.25]; P=0.015) and model 2 (unstandardized β=1.86 [95% CI, 0.42–3.31]; P=0.011). However, the association was attenuated after adjustment for HbA_{1c}, non-HDL cholesterol, and medication status for diabetes and dyslipidemia. We adjusted for antihypertensive medication use instead of the diagnosis of hypertension, and the results were similar (Tables S4 and S5). The differences in sociodemographic and clinical characteristics between the total sample and participants not taking antihypertensive medication are presented in Table S6. We also adjusted for age at brain MRI measurement, and the results were similar (Tables S7 and S8). We reported the unstandardized β for the associations between arterial stiffness and brain structural changes for all participants, as well as for participants not taking antihypertensive medications and subregions of AD signature volume (Tables S9 through S11).

A weak positive correlation between baPWV and CAC was observed (r=0.176; P<0.001). There was no evidence of significant association between MAP and all brain volumes and brain vascular damage: TCBV (unstandardized β=−0.01 [95% CI, −0.35 to 0.33]), gray matter volume (unstandardized β=0.01 [95% CI, −0.19 to 0.21]), AD signature volume (unstandardized β=0.02 [95% CI, −0.004 to 0.04]), prefrontal volume (unstandardized β=−0.04 [95% CI, −0.08 to 0.01]), hippocampus volume (unstandardized β=0.002 [95% CI, −0.004 to 0.008]), and WMHs (unstandardized β=0.03 [95% CI, −0.03 to 0.10]).

DISCUSSION

In this population-based study of Japanese men, higher baPWV was significantly associated with lower AD signature independently of CAC. Higher CAC scores were associated with WMHs independently of baPWV.

These associations were also independent of cardiovascular risk factors including blood pressure, non-HDL cholesterol, and medication status.

Previous studies have shown that greater baPWV was independently associated with brain pathologies including WMHs,[25] β-amyloid deposition,[26] and small-vessel disease.[27] Increased baPWV was associated with lower brain parenchyma fraction, a surrogate index of brain atrophy.[28] A recent study has shown that baPWV was associated with microstructural changes in the white neuronal fiber tracts of the brain.[29] This study also demonstrated the impact of baPWV on white matter integrity in a community-based population. Several brain regions have been highlighted as vulnerable to hemodynamic changes and subsequently may progress into WMHs.[30] Findings from the ARIC (Atherosclerosis Risk in Communities) study showed that higher carotid-femoral PWV (cfPWV) was associated with WMHs and lower AD signature volumes among older adults.[6,7] Among elderly community-dwelling participants diagnosed with AD or mild cognitive impairment,[31] higher cfPWV was also significantly associated with severe medial temporal lobe atrophy that included hippocampus volume. Findings from a systematic review showed that higher arterial stiffness measured by cfPWV and baPWV were associated with greater WMHs.[32] The current study expanded prior knowledge by demonstrating 2 findings. First, cfPWV evaluates central arterial stiffness in the large-sized arteries, whereas baPWV evaluates peripheral arterial stiffness of the medium- to large-sized arteries. cfPWV is a well-established index and provides better estimates of arterial stiffness compared with baPWV.[33] However, baPWV is simpler to assess compared with cfPWV[33] and is a useful screening measure for subclinical arteriosclerosis.[34] The current study demonstrated that higher baPWV was associated with lower AD signatures. Second, prior studies did not simultaneously assess both PWV and CAC and the associations with brain structural changes. We demonstrated that higher arterial stiffness was associated with lower AD signature volume, and the association was independent of cardiovascular risk factors and CAC. Higher blood pressure has been shown to be associated with greater arterial stiffness and lower brain volumes.[35,36] In multivariable models including both baPWV and MAP, we found that higher baPWV, but not MAP, was associated with lower AD signature and hippocampus volumes. This suggests that the association of higher blood pressure with lower brain volume may be explained by greater arterial stiffness.

Several mechanisms underlying the association of arterial stiffness with low brain volumes have been postulated. Arterial stiffness increases pressure and flow pulsatility to the peripheral arteries including small cerebral arteries, resulting in microvascular ischemia or hemorrhage.[4] The stiffening of arteries also can affect hemodynamic stress and cause chronic hypoperfusion, limiting blood flow to the vital organs such as the kidneys and brain.[37] Both mechanisms can cause tissue and microvascular damage,[38,39] seen as brain infarcts and brain atrophy,[5] and the hippocampal neurons may be vulnerable to disturbances of the cerebral circulation.[40,41]

The Rotterdam Study, a prospective population-based study, reported that CAC was positively associated with WMHs.[24] Furthermore, CAC was found to be a predictor for subtle white matter injury of the brain among a healthy population of middle-aged men.[10] In the current study, CAC was entered into the same model including baPWV, which may provide insights into the overall burden of subclinical arteriosclerosis and atherosclerosis on brain structural changes. We observed that CAC was significantly associated with WMHs, but not with brain volumes, independently of cardiovascular risk factors and baPWV. CAC was significantly associated with cognitive decline among Dutch and Icelandic populations, and the association may be explained by WMHs.[9,42] CAC is not only a marker of subclinical atherosclerosis and large-vessel disease but may also be associated with changes to the cerebral vasculature.[43] Shared risk factors associated with both CAC and WMHs, including age, smoking, alcohol intake, hypertension, glucose, and dyslipidemia,[44] may explain the association of CAC with WMHs. Experimental studies demonstrated that cardiovascular risk factors, including hypertension and metabolic abnormalities, result in remodeling of the brain vasculature, including vessel rarefaction, lower vessel caliber, and cerebral blood flow.[45] In the current study, the association of CAC with WMHs remains significant even after adjustment for age; smoking; drinking status; education levels; HbA_{1c}; non-HDL cholesterol; MAP; and medication status for diabetes, hypertension, and dyslipidemia. However, unmeasured risks beyond these factors, including diet and physical activity, may explain the association of CAC with WMHs.[46]

In the sensitivity analysis, after excluding those who were on anti-hypertensive medications, we found similar associations between CAC and brain volumes. Consistent with these findings, we also observed that CAC >0 was significantly associated with WMHs compared with the reference group (CAC=0) after adjustment for covariates in model 2. Meanwhile, only WMHs was significantly associated with arterial stiffness after excluding participants who were on antihypertensive medications. One of the reasons for this difference may be the low sample size in the sensitivity analysis that might reduce the power of the study.

Arterial stiffness assessed by baPWV was associated with increased risk of total CVD events,

cardiovascular death, and all-cause death, as highlighted in the meta-analysis studies.[47,48] Individuals with higher CAC score have significantly increased risk for CVD incidence.[49] Hypertension, diabetes, smoking, and alcohol consumption are common risk factors for both arterial stiffness and atherosclerotic burden.[50,51] Other health conditions, including metabolic syndrome, unhealthy diet, and lack of exercise are well-known risk factors for arterial stiffness.[50] Individuals excessively exposed to these risk factors may have early vascular aging. Stiffening of the arteries alters the normal function of the brain by increasing pulsatile pressure to the microvascular beds, affecting cerebral perfusion and causing microvascular damage.[52] CAC is related to the abnormalities of the small cerebral blood vessels that lead to chronic hemorrhages and lesions in the white matter.[53]

SESSA provides an exceptional opportunity to elucidate these associations in a well-characterized random sample with comprehensive and detailed assessments of subclinical atherosclerosis. This cohort study was conducted among relatively healthy Japanese men who underwent brain MRI.

Our study has limitations. First, brain measures were not obtained when baPWV and CAC assessments were undertaken. There was a 2-year interval between baPWV and CAC measurements and brain MRI measurements for all participants. Therefore, it remains unclear how baPWV and CAC measurements are associated with changes in brain measures over 2 years. However, we also adjusted for age at brain MRI measurement, and the results were similar. Second, the sample included Japanese men only, and the results may not be generalizable to women. Prior studies suggested sex differences in the time course of aging-related arterial stiffness and associated CVD risk, which increases disproportionately in postmenopausal women.[54–56] It remains uncertain whether sex differences exist in the associations of arterial stiffness and CAC with brain measures.

CONCLUSIONS

Higher baPWV was associated with lower AD signature volume among Japanese men independently of cardiovascular risk factors and CAC. Higher CAC scores were associated with WMHs, independently of cardiovascular risk factors and baPWV. From the perspective of clinical practice, our study highlights that arterial stiffness and atherosclerotic burden may contribute to cognitive dysfunction through independent pathways. From a public health perspective, our study emphasizes the importance of preventing and delaying the progression of arterial stiffness and atherosclerotic burden for a healthy brain.

ARTICLE INFORMATION

Received February 17, 2023; accepted April 25, 2023.

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Acknowledgments

The authors thank the participants, investigators, and members of the SESSA research group for their efforts, guidance, and approval for this study.

Sources of Funding

SESSA has been supported by Grants-in-aid for Scientific Research (A) 13307016, (A) 17209023, (A) 21249043, (A) 23249036, (A) 25253046, (A) 15H02528, (A) 18H04074, (B) 26293140 (B) 24790616, (B) 21790579, (B) 18H03048, (C) 23590790, and 15K19225 from the Ministry of Education, Culture, Sports, Science, and Technology Japan; by grant R01HL068200 from the United States' National Institutes of Health/National Heart, Lung, and Blood Institute; and from Glaxo-Smith Kline GB. The funding agencies had no role in study design; in the collection, analysis, or interpretation of data; in writing the report; or in the decision to submit the manuscript for publication.

Disclosures

None.

Supplemental Material

Data S1
Tables S1–S11
Figures S1–S3

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Supplemental Material

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Data S1.

Supplemental Methods

Measurement of brachial-ankle pulse wave velocity

BaPWV was measured on both arms and ankles without clothes. Cuffs were placed on brachia and ankles and the heart sounds were recorded. Pressure waveforms of brachial and tibial arteries were recorded by oscillometric methods using occlusion and sensing cuffs. Cuffs were connected to both plethysmographic sensors and oscillometric pressure sensors that measure the volume pulse form and blood pressure, respectively. Brachial and tibial pressure waveforms were measured simultaneously to determine the time difference between the initial rise in the brachial and tibial waveforms. BaPWV was calculated as the distance between two arterial sites divided by the time difference between waveforms.

Measurement of coronary artery calcification

Images were captured from the level of the aortic root through the heart with a slice thickness of 3.0 mm and scan times of 100 ms for EBCT and 320 ms for MDCT. The images were obtained at 70% of the cardiac cycle using electrocardiogram triggering during a single breath-hold. Quantification of CAC was done using a DICOM workstation and AccuImage software (AccuImage Diagnostics, South San Francisco, California, USA). Peak density and areas of individual coronary calcification were measured. The presence of CAC was determined as a minimum of three contiguous pixels (area= 1 mm^2) with a density of ≥ 130 Hounsfield units (HU).

Assessment of covariates

Current smoker was defined as individuals who smoked tobacco within the last 30 days. Similarly, *current drinker* was classified as individuals who drank alcohol in the past week or month. HbA1c was measured using the latex agglutination immunoassay method according to the Japan Diabetes Society's (JDS) protocol. JDS values were converted into NGSP values using the following equation: NGSP (%) = 1.02 × JDS (%) + 0.25%. Fasting blood glucose was measured by hexokinase glucose-6-phosphate-dehydrogenase enzymatic assay. Fasting serum lipid concentrations were measured by enzymatic methods and were standardized according to the guidelines provided by the United States Centers for Disease Control and Prevention/Cholesterol Reference Method Laboratory Network. Low-density lipoprotein cholesterol (LDL-c) concentration was determined using the Friedewald equation.

Table S1. Multivariable linear regression of the association between arterial stiffness and sub-regions of AD-signature in men of SESSA Study (2010-2014, n=686)

AD signature volume	Model 1 β (95% CI)	*P* value	Model 2 β (95% CI)	*P* value	Model 3 β (95% CI)	*P* value	Model 4 β (95% CI)	*P* value
Entorhinal Cortex	-0.01 (-0.03 to 0.003)	0.119	-0.01 (-0.03 to 0.004)	0.158	-0.01 (-0.03 to 0.01)	0.239	-0.02 (-0.04 to 0.001)	0.069
Parahippocampal	-0.05 (-0.09 to 0.0002)	0.051	-0.04 (-0.09 to 0.004)	0.073	-0.04 (-0.09 to 0.01)	0.116	-0.06 (-0.11 to -0.004)	0.037
Inferior parietal lobule	-0.04 (-0.12 to 0.04)	0.305	-0.04 (-0.12 to 0.04)	0.305	-0.03 (-0.11 to 0.05)	0.408	-0.02 (-0.12 to 0.07)	0.624
Precuneus	-0.08 (-0.20 to 0.03)	0.168	-0.09 (-0.20 to 0.03)	0.143	-0.09 (-0.21 to 0.03)	0.138	-0.13 (-0.27 to 0.002)	0.053
Cuneus	-0.01 (-0.08 to 0.06)	0.768	-0.02 (-0.09 to 0.06)	0.684	-0.003 (-0.08 to 0.07)	0.933	-0.04 (-0.13 to 0.04)	0.329

Data are displayed as standardized betas (β and 95% CI) after fitting linear regression. The one-SD of baPWV was equivalent to 353.6 cm/s. Model 1 includes adjustment for age and TIV. Model 2 includes adjustment for age, TIV, smoking, drinking status and total years of education. Model 3 includes adjustment for age, TIV, smoking, drinking status, total years of education, HbA1c, non-HDL cholesterol and medication status for diabetes and dyslipidemia. Model 4 includes additional adjustment for MAP and medication status for hypertension.

SESSA=Shiga Epidemiological Study of Subclinical Atherosclerosis; baPWV=brachial-ankle pulse wave velocity; AD=Alzheimer's disease; SD=standard deviation; TIV=total intracranial volume; HbA1c=glycated hemoglobin; HDL=high-density lipoprotein; MAP=mean arterial pressure.

Table S2. Multivariable linear regression of the association of baPWV and log CAC with brain structural changes for one-SD increment in baPWV, in 430 men after excluding those who were on antihypertensive medication in the SESSA Study (2010-2014)

	Brain volume					Brain vascular damage
Arterial stiffness	**Total cerebral brain volume β (95% CI)**	**Gray matter volume β (95% CI)**	**AD signature volume β (95% CI)**	**Prefrontal volume β (95% CI)**	**Hippocampus volume β (95% CI)**	**Log white matter hyperintensities β (95% CI)**
Model 1	-1.39 (-6.18 to 3.40)	-1.41 (-4.34 to 1.52)	-0.14 (-0.49 to 0.22)	-0.33 (-0.98 to 0.31)	-0.05 (-0.13 to 0.04)	0.09 (0.05 to 0.13)*
Model 2	-1.59 (-6.45 to 3.28)	-1.47 (-4.41 to 1.47)	-0.15 (-0.51 to 0.21)	-0.39 (-1.04 to 0.26)	-0.04 (-0.13 to 0.04)	0.09 (0.04 to 0.13)*
Model 3	-1.05 (-5.98 to 3.87)	-1.22 (-4.20 to 1.76)	-0.14 (-0.51 to 0.22)	-0.29 (-0.96 to 0.37)	-0.04 (-0.13 to 0.05)	0.08 (0.03 to 0.12)*
Model 4	-0.20 (-5.99 to 5.59)	-0.35 (-3.85 to 3.15)	-0.21 (-0.64 to 0.22)	0.15 (-0.63 to 0.92)	-0.07 (-0.17 to 0.03)	0.06 (0.003 to 0.11)*
Model 5	0.36 (-5.47 to 6.19)	-0.06 (-3.60 to 3.47)	-0.18 (-0.61 to 0.26)	0.24 (-0.55 to 1.03)	-0.07 (-0.17 to 0.04)	0.05 (-0.01 to 0.10)
Log CAC	**Total cerebral brain volume B (95% CI)**	**Gray matter volume B (95% CI)**	**AD signature volume B (95% CI)**	**Prefrontal volume B (95% CI)**	**Hippocampus volume B (95% CI)**	**White matter hyperintensities B (95% CI)**
Model 1	-3.67 (-7.67 to 0.33)	-2.18 (-4.63 to 0.27)	-0.21 (-0.51 to 0.09)	-0.62 (-1.16 to -0.08)*	-0.04 (-0.11 to 0.03)	1.11 (0.41 to 1.82)*
Model 2	-3.08 (-7.11 to 0.96)	-1.60 (-4.05 to 0.85)	-0.16 (-0.46 to 0.14)	-0.52 (-1.06 to 0.02)	-0.03 (-0.10 to 0.04)	1.05 (0.34 to 1.77)*
Model 3	-3.68 (-7.81 to 0.44)	-1.84 (-4.34 to 0.65)	-0.22 (-0.53 to 0.08)	-0.53 (-1.09 to 0.03)	-0.04 (-0.11 to 0.03)	1.05 (0.32 to 1.77)*
Model 4	-3.57 (-7.72 to 0.58)	-1.70 (-4.21 to 0.82)	-0.23 (-0.54 to 0.08)	-0.47 (-1.02 to 0.09)	-0.04 (-0.12 to 0.03)	0.99 (0.26 to 1.73)*
Model 5	-3.78 (-7.97 to 0.42)	-1.75 (-4.30 to 0.80)	-0.22 (-0.53 to 0.09)	-0.50 (-1.07 to 0.06)	-0.04 (-0.11 to 0.04)	0.97 (0.23 to 1.70)*

Data are displayed as standardized betas (β and 95% CI) for baPWV and unstandardized betas (B and 95% CI) for log CAC. The one-SD of baPWV was equivalent to 345.5 cm/s. CAC was transformed as log (CAC+1). Model 1 includes

adjustment for age and TIV (additional adjustment of CT-type for log CAC analysis). Model 2 includes adjustment for age, TIV, smoking, drinking status and total years of education. Model 3 includes adjustment for age, TIV, smoking, drinking status, total years of education, HbA1c, non-HDL cholesterol and medication status for diabetes and dyslipidemia. Model 4 includes additional adjustment for MAP and medication status for hypertension. Model 5 was inclusion of both baPWV and CAC simultaneously in the same model.

*****P<0.05.

baPWV=brachial-ankle pulse wave velocity; CAC=coronary artery calcification; SD=standard deviation; SESSA=Shiga Epidemiological Study of Subclinical Atherosclerosis; AD=Alzheimer's disease; TIV=total intracranial volume; CT=computerized tomography; HbA1c=glycated hemoglobin; HDL=high-density lipoprotein; MAP=mean arterial pressure.

Table S3. Adjusted *B* on the association between CAC>0 and brain structural changes in men of SESSA Study (2010=2014, n=686)

	Brain volume (ml)					Brain vascular damage
CAC>0	Total cerebral brain volume B (95% CI)	Gray matter volume B (95% CI)	AD signature volume B (95% CI)	Prefrontal volume B (95% CI)	Total hippocampus B (95% CI)	White matter hyperintensities B (95% CI)
Model 1	-1.40 (-8.71 to 5.91)	-0.53 (-4.91 to 3.85)	-0.08 (-0.60 to 0.44)	-0.44 (-1.44 to 0.55)	-0.01 (-0.13 to 0.12)	1.80 (0.36 to 3.25)*
Model 2	-1.33 (-8.63 to 5.98)	-0.49 (-4.82 to 3.84)	-0.07 (-0.59 to 0.45)	-0.42 (-1.40 to 0.57)	-0.01 (-0.13 to 0.12)	1.86 (0.42 to 3.31)*
Model 3	-0.67 (-8.07 to 6.73)	0.13 (-4.25 to 4.51)	-0.11 (-0.64 to 0.42)	-0.28 (-1.29 to 0.73)	-0.01 (-0.14 to 0.12)	1.34 (-0.11 to 2.80)
Model 4	-0.26 (-7.77 to 7.24)	0.24 (-4.20 to 4.68)	-0.17 (-0.71 to 0.36)	-0.10 (-1.12 to 0.91)	-0.02 (-0.15 to 0.11)	1.12 (-0.35 to 2.59)
Model 5	-0.07 (-7.59 to 7.46)	0.40 (-4.05 to 4.85)	-0.14 (-0.67 to 0.40)	-0.07 (-1.09 to 0.95)	-0.01 (-0.14 to 0.12)	1.07 (-0.40 to 2.54)

Data are displayed as unstandardized betas (B and 95% CI). CAC=0 is the reference group. Model 1 includes adjustment for age, TIV and CT-type. Model 2 includes adjustment for age, TIV, CT-type, smoking, drinking status and total years of education. Model 3 includes adjustment for age, TIV, CT-type, smoking, drinking status, total years of education, HbA1c, non-HDL cholesterol and medication status for diabetes and dyslipidemia. Model 4 includes additional adjustment for MAP and medication status for hypertension. Model 5 was inclusion of both baPWV and CAC simultaneously in the same model. *****P<0.05.

CAC=coronary artery calcification; SESSA=Shiga Epidemiological Study of Subclinical Atherosclerosis; AD=Alzheimer's disease; TIV=total intracranial volume; CT=computerized tomography; HbA1c=glycated hemoglobin; HDL=high-density lipoprotein; MAP=mean arterial pressure; baPWV=brachial-ankle pulse wave velocity.

Table S4. Associations between arterial stiffness and brain structural changes among men in the SESSA Study (2010-2014, n=686)

	Standardized beta β (95% CI)		Unstandardized beta B (95% CI)	
Brain structural changes	**Model adjusted for covariates plus diagnosis of hypertension**	**Model adjusted for covariates plus antihypertensive medication use**	**Model adjusted for covariates plus diagnosis of hypertension**	**Model adjusted for covariates plus antihypertensive medication use**
Total cerebral brain volume	-1.78 (-5.78 to 2.22)	-1.56 (-5.93 to 2.80)	-0.01 (-0.02 to 0.006)	-0.004 (-0.02 to 0.01)
Gray matter volume	-1.36 (-3.72 to 1.01)	-1.35 (-3.93 to 1.24)	-0.004 (-0.01 to 0.003)	-0.004 (-0.01 to 0.004)
AD signature volume	-0.28 (-0.56 to -0.01)	-0.33 (-0.64 to -0.02)*	-0.001 (-0.002 to 0.00002)	-0.001 (-0.002 to -0.0001)*
Prefrontal volume	-0.45 (-0.99 to 0.09)	-0.29 (-0.88 to 0.30)	-0.001 (-0.003 to 0.0003)	-0.001 (-0.002 to 0.001)
Hippocampus volume	-0.08 (-0.15 to -0.007)*	-0.07 (-0.15 to 0.002)	-0.0002 (-0.0004 to -0.00002)*	-0.0002 (-0.0004 to 0.000004)
Log white matter hyperintensities	0.05 (0.01 to 0.08)*	0.04 (-0.004 to 0.07)	0.0001 (0.00003 to 0.0002)*	0.0001 (-0.00001 to 0.0002)

Data are displayed as standardized betas (β and 95% CI) for a one-SD increment of 353.6 cm/s in baPWV and unstandardized betas (B and 95% CI) in multivariable linear regression models. Hypertension was diagnosed as having SBP ≥140 mmHg, or DBP ≥90 mmHg, and/or use of antihypertensive medication. Covariates included age, TIV, smoking, drinking status, total years of education, HbA1c, non-HDL cholesterol, CAC and medication status for diabetes and dyslipidemia. ***P*<0.05.

SESSA=Shiga Epidemiological Study of Subclinical Atherosclerosis; baPWV=brachial-ankle pulse wave velocity; AD=Alzheimer's disease; SD=standard deviation; SBP=systolic blood pressure; DBP=diastolic blood pressure; TIV=total intracranial volume; HbA1c=glycated hemoglobin; HDL=high-density lipoprotein; CAC=coronary artery calcification.

Table S5. Associations between CAC and brain structural changes among men in the SESSA Study (2010-2014, n=686)

Brain structural changes (ml)	B (95% CI)	
	Model adjusted for covariates plus diagnosis of hypertension	Model adjusted for covariates plus antihypertensive medication use
Total cerebral brain volume	-2.16 (-5.40 to 1.08)	-2.09 (-5.35 to 1.17)
Gray matter volume	-0.99 (-2.91 to 0.92)	-1.02 (-2.95 to 0.91)
AD signature volume	-0.15 (-0.38 to 0.08)	-0.17 (-0.40 to 0.07)
Prefrontal volume	-0.21 (-0.65 to 0.23)	-0.19 (-0.63 to 0.25)
Hippocampus volume	-0.03 (-0.08 to 0.03)	-0.03 (-0.08 to 0.03)
White matter hyperintensities	0.70 (0.06 to 1.33)*	0.68 (0.05 to 1.32)*

Data are displayed as unstandardized betas (B and 95% CI) for one unit of log CAC in multivariable linear regression models. Hypertension was diagnosed as having SBP ≥140 mmHg, or DBP ≥90 mmHg, and/or use of antihypertensive medication. Covariates included age, TIV, CT-type, smoking, drinking status, total years of education, HbA1c, non-HDL cholesterol, baPWV and medication status for diabetes and dyslipidemia. *****P<0.05.

CAC=coronary artery calcification; SESSA=Shiga Epidemiological Study of Subclinical Atherosclerosis; AD=Alzheimer's disease; SBP=systolic blood pressure; DBP=diastolic blood pressure; TIV=total intracranial volume; CT=computerized tomography; HbA1c=glycated hemoglobin; HDL=high-density lipoprotein; baPWV=brachial-ankle pulse wave velocity.

Table S6. Differences in sociodemographic and clinical characteristics between the total sample and participants not taking antihypertensive medication in the SESSA Study (2010-2014), Shiga, Japan

Clinical characteristics	Total sample (n=686)	Participants not taking antihypertensive medication (n=430)	*P* value
Age, years, mean ± SD	67.9 ± 8.4	67.0 ± 9.0	0.086
Education, years, mean ± SD	12.0 ± 4.0	12.7 ± 4.0	0.904
Current smoker, n (%)	135 (19.7)	95 (22.1)	0.426
Current drinker, n (%)	560 (81.6)	347 (80.7)	0.883
BMI, kg/m^2, mean ± SD	23.3 ± 2.9	22.7 ± 2.8	0.002
SBP, mmHg, mean ± SD	131.8 ± 16.8	130.5 ± 17.4	0.238
DBP, mmHg, mean ± SD	77.2 ± 10.5	77.1 ± 10.6	0.864
MAP, mmHg, mean ± SD	95.4 ± 11.5	94.9 ± 11.8	0.497
Heart rate, bpm, mean ± SD	64.6 ± 10.5	64.0 ± 9.8	0.340
Total cholesterol, mg/dL, mean ± SD	202.8 ± 34.0	205.5 ± 35.9	0.217
Triglycerides, mg/dL, median (IQR)	101.0 (70.0)	98.5 (69.0)	0.319
HDL-c, mg/dL, mean ± SD	59.5 ± 16.5	61.0 ± 16.6	0.144
LDL-c, mg/dL, mean ± SD	118.9 ± 31.9	120.8 ± 33.6	0.344
non-HDL-c, mg/dL, mean ± SD	143.3 ± 32.6	144.5 ±34.7	0.576
HbA1c NGSP, %, mean ± SD	5.91 ± 0.8	5.9 ± 0.8	0.306
Antihypertensive medication, n (%)	256 (37.3)	-	-
Antidiabetic medication, n (%)	102 (14.9)	44 (10.2)	0.025
Medication for dyslipidemia, n (%)	141 (20.6)	58 (13.5)	0.003
Hypertension, n (%)	378 (55.1)	122 (28.4)	<0.001
Diabetes, n (%)	143 (20.9)	68 (15.8)	0.037
Dyslipidemia, n (%)	388 (56.6)	225 (52.3)	0.167
baPWV, cm/s, mean ± SD	1728.5 ± 353.6	1684.9 ± 345.5	0.043
CAC score, median (IQR)	26.3 (166.5)	12.9 (132.7)	0.016

All values are presented as means ± SD for continuous variables except for triglycerides and CAC score, median (IQR). Frequencies and percentages are presented for categorical variables. *P* values for between-group comparisons were analyzed by independent t-test for continuous variables and chi-square test for categorical variables.
SESSA=Shiga Epidemiological Study of Subclinical Atherosclerosis; SD=standard deviation; BMI=body mass index; SBP=systolic blood pressure; DBP=diastolic blood pressure; MAP=mean arterial pressure; bpm=beats-per-minute; IQR=interquartile range; HDL-c=high-density lipoprotein cholesterol; LDL-c=low-density lipoprotein cholesterol; HbA1c NGSP=glycated hemoglobin according to the National Glycohemoglobin Standardization Program; baPWV=brachial-ankle pulse wave velocity; CAC=coronary artery calcification.

Table S7. Associations between arterial stiffness and brain structural changes among men in the SESSA Study (2010-2014, n=686)

	Standardized beta β (95% CI)		Unstandardized beta B (95% CI)	
Brain structural changes	**Model adjusted for covariates plus age at baPWV and CAC measurements**	**Model adjusted for covariates plus age at brain MRI measurement**	**Model adjusted for covariates plus age at baPWV and CAC measurements**	**Model adjusted for covariates plus age at brain MRI measurement**
Total cerebral brain volume	-1.56 (-5.93 to 2.80)	-1.53 (-5.90 to 2.83)	-0.004 (-0.02 to 0.01)	-0.004 (-0.02 to 0.01)
Gray matter volume	-1.35 (-3.93 to 1.24)	-1.29 (-3.86 to 1.29)	-0.004 (-0.01 to 0.004)	-0.004 (-0.01 to 0.004)
AD signature volume	-0.33 (-0.64 to -0.02)*	-0.32 (-0.63 to -0.01)*	-0.001 (-0.002 to -0.0001)*	-0.001 (-0.002 to -0.00004)*
Prefrontal volume	-0.29 (-0.88 to 0.30)	-0.27 (-0.86 to 0.31)	-0.001 (-0.002 to 0.001)	-0.001 (-0.002 to 0.001)
Hippocampus volume	-0.07 (-0.15 to 0.002)	-0.07 (-0.15 to 0.001)	-0.0002 (-0.0004 to 0.000004)	-0.0002 (-0.0004 to 0.000004)
Log white matter hyperintensities	0.04 (-0.004 to 0.07)	0.04 (-0.004 to 0.07)	0.0001 (-0.00001 to 0.0002)	0.0001 (-0.00001 to 0.0002)

Data are displayed as standardized betas (β and 95% CI) for a one-SD increment of 353.6 cm/s in baPWV and unstandardized betas (B and 95% CI) in multivariable linear regression models. Covariates included TIV, smoking, drinking status, total years of education, HbA1c, non-HDL cholesterol, MAP, CAC and medication status for diabetes, hypertension and dyslipidemia. ***P***<0.05.

SESSA=Shiga Epidemiological Study of Subclinical Atherosclerosis; baPWV=brachial-ankle pulse wave velocity; CAC=coronary artery calcification; MRI=magnetic resonance imaging; AD=Alzheimer's disease; SD=standard deviation; TIV=total intracranial volume; HbA1c=glycated hemoglobin; HDL=high-density lipoprotein; MAP=mean arterial pressure.

Table S8. Associations between CAC and brain structural changes among men in the SESSA Study (2010-2014, n=686)

	B (95% CI)	
Brain structural changes (ml)	**Model adjusted for covariates plus age at baPWV and CAC measurements**	**Model adjusted for covariates plus age at brain MRI measurement**
Total cerebral brain volume	-2.09 (-5.35 to 1.17)	-2.12 (-5.38 to 1.13)
Gray matter volume	-1.02 (-2.95 to 0.91)	-1.02 (-2.95 to 0.90)
AD signature volume	-0.17 (-0.40 to 0.07)	-0.17 (-0.40 to 0.07)
Prefrontal volume	-0.19 (-0.63 to 0.25)	-0.19 (-0.63 to 0.25)
Hippocampus volume	-0.03 (-0.08 to 0.03)	-0.03 (-0.08 to 0.03)
White matter hyperintensities	0.68 (0.05 to 1.32)*	0.69 (0.06 to 1.33)*

Data are displayed as unstandardized betas (B and 95% CI) for one unit of log CAC in multivariable linear regression models. Covariates included TIV, CT-type, smoking, drinking status, total years of education, HbA1c, non-HDL cholesterol, MAP, baPWV and medication status for diabetes, hypertension and dyslipidemia. ***P*<0.05.

CAC=coronary artery calcification; SESSA=Shiga Epidemiological Study of Subclinical Atherosclerosis; baPWV=brachial-ankle pulse wave velocity; MRI=magnetic resonance imaging; AD=Alzheimer's disease; TIV=total intracranial volume; CT=computerized tomography; HbA1c=glycated hemoglobin; HDL=high-density lipoprotein; MAP=mean arterial pressure.

Table S9. Unstandardized beta on the association between arterial stiffness and brain structural changes in men of SESSA Study (2010-2014, n=686)

	Brain volume (ml)					Brain vascular damage
Arterial stiffness	**Total cerebral brain volume B (95% CI)**	**Gray matter volume B (95% CI)**	**AD signature volume B (95% CI)**	**Prefrontal volume B (95% CI)**	**Hippocampus volume B (95% CI)**	**Log white matter hyperintensities B (95% CI)**
Model 1	-0.08 (-0.10 to -0.06)*	-0.04 (-0.05 to -0.03)*	-0.004 (-0.01 to -0.003)*	-0.008 (-0.01 to -0.006)*	-0.001 (-0.001 to -0.0009)*	0.0007 (0.0006 to 0.0008)*
Model 2	-0.01 (-0.02 to 0.002)	-0.006 (-0.01 to 0.0001)	-0.0008 (-0.002 to -0.00002)*	-0.002 (-0.003 to -0.0004)*	-0.0002 (-0.0004 to -0.00005)*	0.0002 (0.0001 to 0.0003)*
Model 3	-0.01 (-0.02 to 0.007)	-0.004 (-0.01 to 0.003)	-0.001 (-0.002 to -0.0001)*	-0.001 (-0.003 to 0.001)	-0.0002 (-0.0004 to -0.00001)*	0.0001 (0.000004 to 0.0002)*
Model 4	-0.004 (-0.02 to 0.01)	-0.004 (-0.01 to 0.004)	-0.001 (-0.002 to -0.0001)*	-0.001 (-0.002 to 0.001)	-0.0002 (-0.0004 to 0.000004)	0.0001 (-0.00001 to 0.0002)

Data are displayed as unstandardized betas (B and 95% confidence interval) after fitting linear regression. Model 1 was unadjusted. Model 2 includes adjustment for age and TIV. Model 3 includes adjustment for age, TIV, smoking, drinking status, total years of education, HbA1c, non-HDL cholesterol, MAP and medication status for diabetes, hypertension and dyslipidemia. Model 4 was inclusion of both baPWV and CAC simultaneously in the same model, adjusted for all covariates that were included in Model 3.

*****P<0.05.

SESSA=Shiga Epidemiological Study of Subclinical Atherosclerosis; AD=Alzheimer's disease; TIV=total intracranial volume; HbA1c=glycated hemoglobin; HDL=high-density lipoprotein; MAP=mean arterial pressure; baPWV=brachial-ankle pulse wave velocity; CAC=coronary artery calcification.

Table S10. Unstandardized beta on the association between arterial stiffness and sub-regions of AD-signature in men of SESSA Study (2010-2014, n=686)

AD signature volume (ml)	Model 1 B (95% CI)	*P* value	Model 2 B (95% CI)	*P* value	Model 3 B (95% CI)	*P* value	Model 4 B (95% CI)	*P* value
Entorhinal Cortex	-0.00004 (-0.0001 to 0.00001)	0.119	-0.00003 (-0.0001 to 0.00001)	0.158	-0.00003 (-0.0001 to 0.00002)	0.239	-0.00005 (-0.0001 to 0.000004)	0.069
Parahippocampal	-0.0001 (-0.0003 to 0.000001)	0.051	-0.0001 (-0.0003 to 0.00001)	0.073	-0.0001 (-0.0002 to 0.00003)	0.116	-0.0002 (-0.0003 to -0.00001)	0.037
Inferior parietal lobule	-0.0001 (-0.0003 to 0.0001)	0.305	-0.0001 (-0.0003 to 0.0001)	0.305	-0.0001 (-0.0003 to 0.0001)	0.408	-0.0001 (-0.0003 to 0.0002)	0.624
Precuneus	-0.0002 (-0.001 to 0.0001)	0.168	-0.0002 (-0.001 to 0.00008)	0.143	-0.0003 (-0.001 to 0.0001)	0.138	-0.0004 (-0.001 to 0.00001)	0.053
Cuneus	-0.00003 (-0.0002 to 0.0002)	0.768	-0.00004 (-0.0002 to 0.0002)	0.684	-0.00001 (-0.0002 to 0.0002)	0.933	-0.0001 (-0.0004 to 0.0001)	0.329

Data are displayed as unstandardized betas (B and 95% CI) after fitting linear regression. Model 1 includes adjustment for age and TIV. Model 2 includes adjustment for age, TIV, smoking, drinking status and total years of education. Model 3 includes adjustment for age, TIV, smoking, drinking status, total years of education, HbA1c, non-HDL cholesterol and medication status for diabetes and dyslipidemia. Model 4 includes additional adjustment for MAP and medication status for hypertension.

AD=Alzheimer's disease; SESSA=Shiga Epidemiological Study of Subclinical Atherosclerosis; TIV=total intracranial volume; HbA1c=glycated hemoglobin; HDL=high-density lipoprotein; MAP=mean arterial pressure.

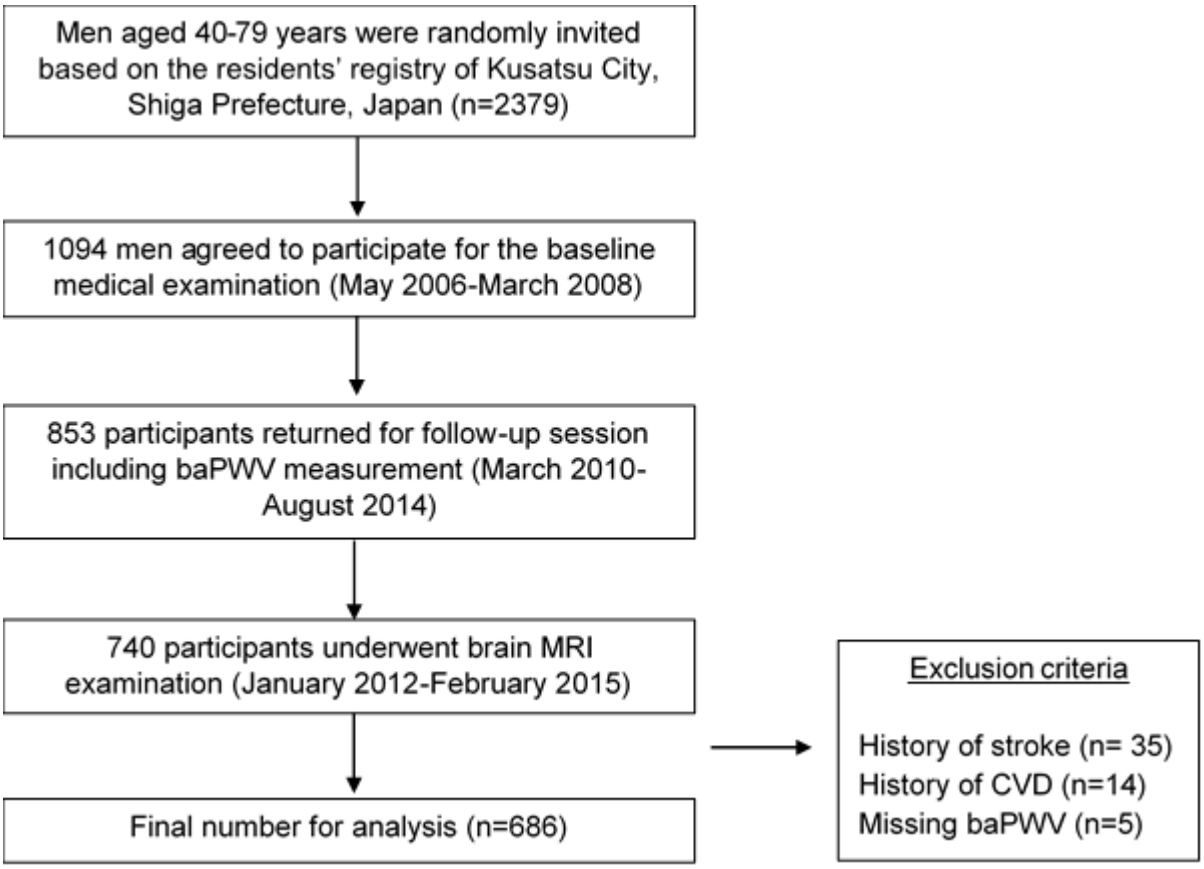
Table S11. Unstandardized beta on the association between arterial stiffness and brain structural changes, in 430 men after excluding those who were on antihypertensive medication in the SESSA Study (2010-2014)

	Brain volume (ml)					Brain vascular damage
Arterial stiffness	**Total cerebral brain volume B (95% CI)**	**Gray matter volume B (95% CI)**	**AD signature volume B (95% CI)**	**Prefrontal volume B (95% CI)**	**Hippocampus volume B (95% CI)**	**Log white matter hyperintensities B (95% CI)**
Model 1	-0.004 (-0.02 to 0.01)	-0.004 (-0.01 to 0.004)	-0.0004 (-0.001 to 0.0006)	-0.001 (-0.003 to 0.001)	-0.0001 (-0.0004 to 0.0001)	0.0003 (0.0001 to 0.0004)*
Model 2	-0.004 (-0.02 to 0.01)	-0.004 (-0.01 to 0.004)	-0.0004 (-0.001 to 0.001)	-0.001 (-0.003 to 0.001)	-0.0001 (-0.0004 to 0.0001)	0.0002 (0.0001 to 0.0004)*
Model 3	-0.003 (-0.02 to 0.01)	-0.003 (-0.01 to 0.005)	-0.0004 (-0.001 to 0.001)	-0.001 (-0.003 to 0.001)	-0.0001 (-0.0004 to 0.0001)	0.0002 (0.0001 to 0.0003)*
Model 4	-0.001 (-0.02 to 0.02)	-0.001 (-0.01 to 0.01)	-0.001 (-0.002 to 0.001)	0.0004 (-0.002 to 0.003)	-0.0002 (-0.0005 to 0.0001)	0.0002 (0.00001 to 0.0003)*
Model 5	0.001 (-0.02 to 0.02)	-0.0002 (-0.01 to 0.01)	-0.001 (-0.002 to 0.001)	0.001 (-0.002 to 0.003)	-0.0002 (-0.0005 to 0.0001)	0.0001 (-0.00002 to 0.0003)

Data are displayed as unstandardized betas (B and 95% CIs). Model 1 includes adjustment for age and TIV. Model 2 includes adjustment for age, TIV, smoking, drinking status and total years of education. Model 3 includes adjustment for age, TIV, smoking, drinking status, total years of education, HbA1c, non-HDL cholesterol and medication status for diabetes and dyslipidemia. Model 4 includes additional adjustment for MAP and medication status for hypertension. Model 5 was inclusion of both baPWV and CAC simultaneously in the same model.

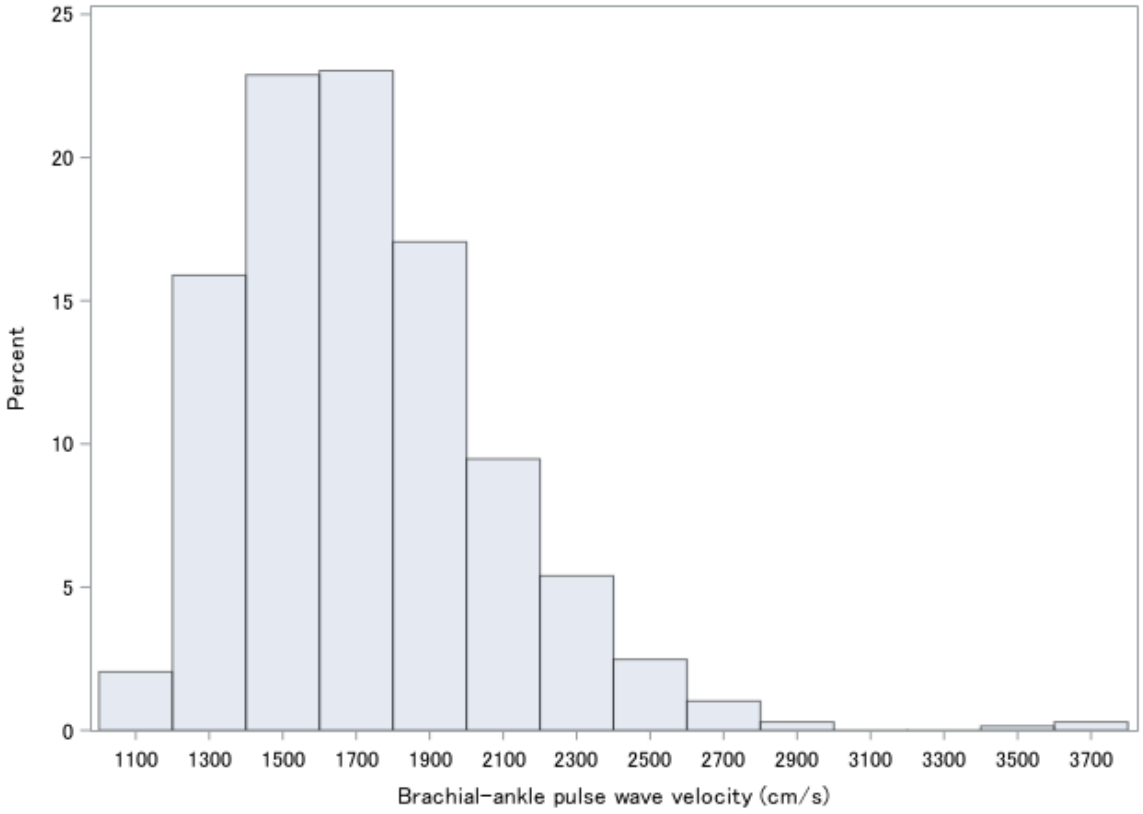
*****P<0.05. SESSA=Shiga Epidemiological Study of Subclinical Atherosclerosis; AD=Alzheimer's disease; TIV=total intracranial volume; HbA1c=glycated hemoglobin; HDL=high-density lipoprotein; MAP=mean arterial pressure; baPWV=brachial-ankle pulse wave velocity; CAC=coronary artery calcification.

Figure S1. Participant flowchart



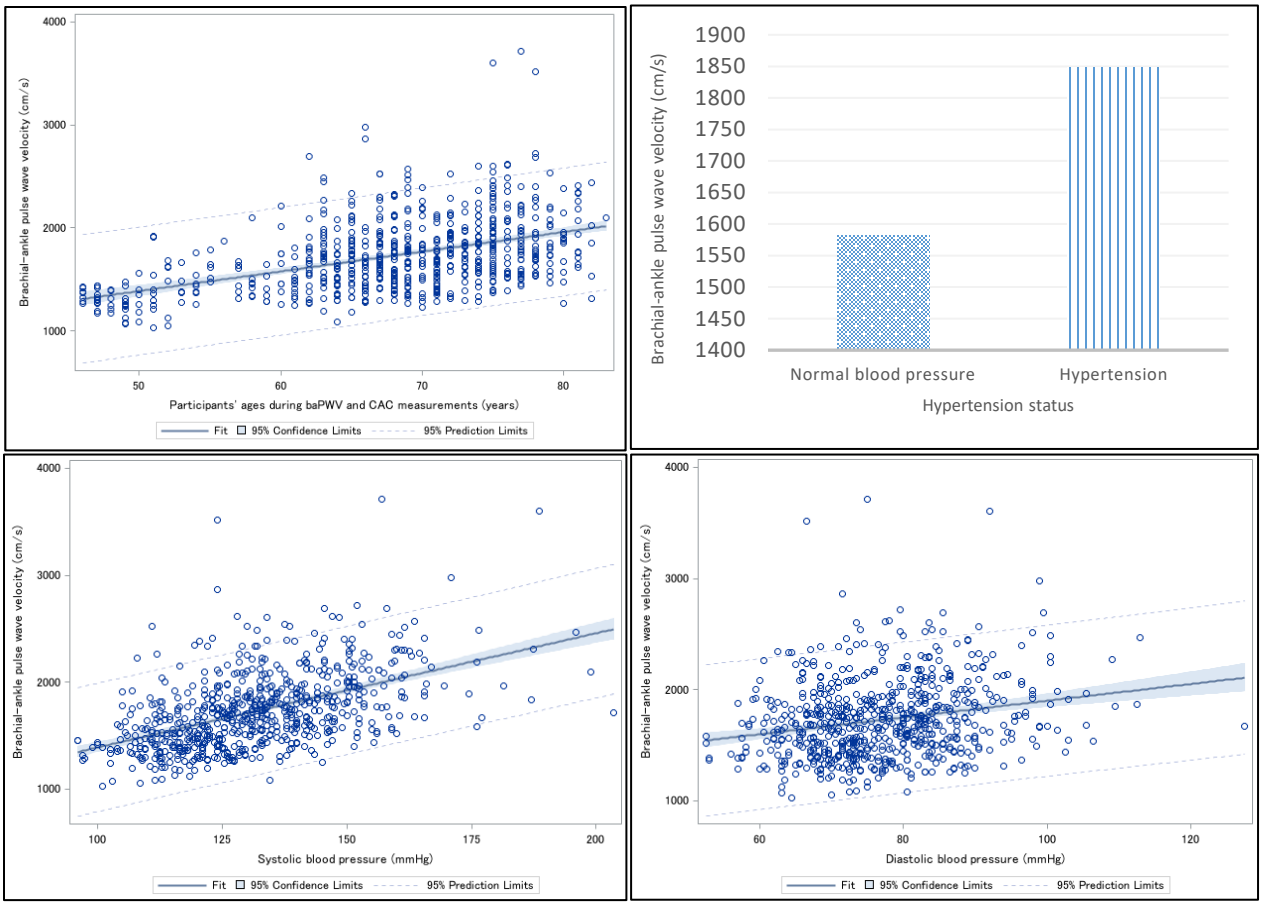
baPWV=brachial-ankle pulse wave velocity; MRI=magnetic resonance imaging; CVD=cardiovascular disease.

Figure S2. Distribution of brachial-ankle pulse wave velocity among men of the SESSA Study (2010-2014, n=686)



SESSA=Shiga Epidemiological Study of Subclinical Atherosclerosis.

Figure S3. Distribution of participants' ages, hypertension status, systolic and diastolic blood pressure with baPWV among men of the SESSA Study (2010-2014, n=686)



baPWV=brachial-ankle pulse wave velocity; CAC=coronary artery calcification; SESSA=Shiga Epidemiological Study of Subclinical Atherosclerosis.