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Original Article

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Relationship of Four Blood Pressure Indexes to Subclinical Cerebrovascular Diseases Assessed by Brain MRI in General Japanese Men

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Aim: The relationship of blood pressure (BP) indexes (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse pressure [PP], mean arterial pressure [MAP]) to subclinical cerebrovascular diseases (SCVDs) remains unclear. This study aimed to elucidate the relationship of four BP indexes measured at two visits on SCVDs assessed by magnetic resonance imaging (MRI) in general Japanese men.

Methods: In general Japanese men aged 40–79 years (*N*=616), office BP indexes were measured at two visits (Visits 1 [2006–2008] and 2 [2010–2014]). MRI images obtained on the third visit (2012–2015) were examined for prevalent SCVDs: lacunar infarction, periventricular hyperintensity (PVH), deep subcortical white matter hyperintensity (DSWMH), microbleeds, and intracranial artery stenosis (ICAS). Using a multivariable logistic regression analysis, we computed and estimated the odds ratio of each prevalent SCVD for one standard deviation higher BP indexes. The same analyses were performed using home BP.

Results: All four office BP indexes at both visits associated with lacunar infarction. Visit 1 and 2 DBP and Visit 1 MAP associated with PVH and DSWMH, and Visit 1 SBP associated with DSWMH. All Visit 2 BP indexes appear to show stronger association with microbleeds than Visit 1 indexes, and Visit 1 and 2 SBP, PP, and MAP showed similar associations with ICAS. Additional analyses using home BP indexes revealed similar relationships; however, the significance of some relationships decreased.

Conclusion: In general Japanese men, BP indexes were associated with most of SCVDs, and BP indexes measured at different periods associated with different SCVDs assessed by MRI.

Key words: Blood pressure indexes, Home blood pressure, Brain magnetic resonance imaging, Subclinical cerebrovascular diseases, Japanese

Introduction

Subclinical cerebrovascular diseases (SCVDs) are early brain conditions without clinical manifestations and are the most common neuroimaging incidental findings in the elderly[1)]. With the advancement in brain imaging technology, these minute changes in the brain may be easily detected by neuroimaging scans using magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA). These incidental findings have been identified as silent MRI markers of stroke in the elderly[1, 2)].

Increased blood pressure (BP) is an important and modifiable risk factor for cerebral small vessel

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disease, which falls under the wider term SCVDs. Previous findings showed that high BP levels were associated with each of the MRI markers of SCVDs[2]. Four BP indexes, namely, systolic BP (SBP), diastolic BP (DBP), pulse pressure (PP), and mean arterial pressure (MAP), have been identified as strong predictors of stroke, myocardial infarction, and cardiovascular mortality[3-7]. Furthermore, relationships were reported between different BP indexes and several SCVDs using MRI markers[8-11].

However, findings on the effect size of BP indexes and SCVDs are controversial, and the pathophysiological mechanisms of each BP index in SCVDs remain unclear. Further epidemiological investigations with different study designs are needed to clarify these relationships[11-15]. The results of this study may provide a more detailed understanding of the pathophysiological mechanisms of BP indexes in SCVDs.

Aim

This study aims to clarify the effect size of BP indexes from two different periods on SCVD outcomes assessed by MRI in general Japanese men.

Methods

Study Population

The Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA) is an observational, community-based, prospective study on randomly selected Japanese men from Kusatsu City, Shiga, Japan. The total number of participants at Visit 1 [2006–2008] between the ages of 40–79 years was 1094 and that at Visit 2 [2010–2014] was 853. All participants from Visit 2 were invited for a third visit (MRI visit) [2012–2015] and 740 complied. Informed consent was provided by all participants, and explicit details on the SESSA study were previously described[12, 13]. Participants with missing values in home BP measurements ($n=85$), MR scans ($n=1$), and cerebrovascular risk factors ($n=3$) were excluded. In addition, participants with a history of myocardial infarction and stroke with symptoms at each visit [Visit 1, myocardial infarction ($n=7$), stroke ($n=15$); Visit 2, myocardial infarction ($n=6$), stroke ($n=7$)] were excluded prior to statistical analyses. The number of participants remaining after these exclusion criteria was 616.

The cerebrovascular risk factors measured or obtained from self-administered questionnaires at Visits 1 and 2 were as follows: body mass index (BMI) defined by weight (kg) divided by height squared (m^2); smoking and drinking statuses categorized into current, past, and never; and the use of antihypertensive, diabetes mellitus, and lipid-lowering medication[16]. The latex agglutination inhibition assay (Kyowa Medix, Tokyo, Japan) was used to measure hemoglobin A1c (HbA1c) according to the methods of either the Japan Diabetes Society (JDS) protocol or the National Glycohemoglobin Standardization Program (NGSP)[17]. Using the equation recommended by the JDS, NGSP values were obtained by converting JDS values as follows: NGSP (%) = 1.02 × JDS (%) + 0.25%. Serum total cholesterol, triglyceride, and high density lipoprotein cholesterol (HDL-C) levels were measured as previously described[12, 13, 16]. Low density lipoprotein cholesterol (LDL-C) (mg/dL) levels were calculated by the Friedewald equation (serum total cholesterol minus HDL-C minus triglycerides/5), when triglyceride concentrations were less than 400 mg/dL.

BP Measurements

BP was measured at Visits 1 and 2 clinically at the office by a trained nurse according to the criteria of The Japanese Society of Hypertension Guidelines for the Management of Hypertension[12]. Briefly, BP was measured in the morning twice consecutively within a 30-s interval by the nurse using an automated sphygmomanometer (BP-8800; Colin Medical Technology, Komaki, Japan) with an appropriate cuff size on the right arm after participants had been in the seated position resting for 5 min.

Four BP indexes (SBP, DBP, PP, and MAP) were measured and calculated separately at Visits 1 and 2. Average SBP and DBP were the averages of the two readings. PP was defined as average SBP minus average DBP, while MAP was calculated as SBP/3+2DBP/3[5].

BP measured at home was recorded using an automatic sphygmomanometer (HEM-705 IT Fuzzy Cuff, Omron Healthcare Co., Ltd.). Participants measured their BP once in the morning for 7 consecutive days, within 1 h of waking up, after urination, before breakfast, before taking any medications, and in the seated position after resting for 2 min[12, 18]. The

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average of 7 days morning SBP, and those of 7 days morning DBP was used and the same BP indexes were calculated for home BP.

Brain MRI Assessment and Outcome Classification

All brain MRI and MRA were performed using a 1.5-Tesla MRI scanner (Signa HDxt 1.5T ver. 16; GE Healthcare, Milwaukee, Wisconsin). Three-dimensional T1-weighted spoiled gradient-recalled (SPGR), two-dimensional T2- and T2*-weighted, fluid-attenuated inversion-recovery (FLAIR), and time-of-flight (TOF) MRA images were obtained to diagnose small vessel disease and cerebral artery stenosis. T2- and T2*-weighted and FLAIR images were all obtained at a thickness of 4 mm with no inter-slice gaps. Two neurosurgeons (KN, AS), certified by the Japan Neurosurgery Society, independently assessed all images obtained using MRA/MRI in duplicate without knowledge of participant characteristics. Disagreements in assessments were resolved with adjudication by neurosurgeons.

The outcomes of SCVDs were defined and graded as follows: lacunar infarction was defined as an area of low signal intensity on T1-weighted images, with a size of 3 to 15 mm, that was visible as a hyperintense lesion on T2-weighted images. The irregular shape of lacunar infarcts in SPGR and surrounding gliosis in FLAIR images were considered when differentiating these lesions from an enlarged perivascular space. In each anatomical segment (the basal ganglia, brainstem, thalamus, white matter, and other areas), lacunar infarcts were counted and graded as follows: 0, 1 to 2, ≥ 3 [19].

White matter lesions were defined as hyperintense regions on FLAIR images, sub-grouped to either periventricular hyperintensity (PVH) or deep subcortical white matter hyperintensity (DSWMH), and then graded according to the classification proposed by Shinohara and colleagues [20]. This classification was adopted by the Japanese Braindock Guidelines in 2014 and is similar to that by Fazekas [21, 22]. PVH was graded as follows: no lesion or only a periventricular rim (grade 0), localized PVH, such as a periventricular cap (grade 1), slightly thick PVH covering the periventricular area (grade 2), diffused PVH expanding to deep white matter lesions (grade 3), and large PVH expanding to deep white matter or subcortex lesions (grade 4). DSWMH was graded as follows: no lesion (grade 0), a spotty clear-boundary lesion with a maximum diameter of less than 3 mm or an enlarged perivascular cavity (grade 1), patchy and scattered lesions on the subcortex to deep white matter with a maximum diameter of more than 3 mm (grade 2), a deep white matter lesion with a fused unclear boundary (grade 3), and a large fused white matter lesion (grade 4).

Microbleeds were defined as hypointense (or signal void) lesions on T2*-weighted images. The number of microbleeds was counted for each of the following anatomical segments: basal ganglia, cerebellum, cerebral cortex, brainstem, thalamus, and white matter.

Intracranial artery stenosis (ICAS) was assessed in 11 intracranial arteries [the basilar artery plus 5 vessels bilaterally: intracranial segments of the internal carotid artery (ICA), the middle cerebral artery (MCA), anterior cerebral artery (ACA), intracranial segments of the vertebral artery, and the posterior cerebral artery (PCA)]. Using criteria established in the Warfarin–Aspirin Symptomatic Intracranial Disease trial [23], the ordinal degree of narrowing in each artery was graded as follows: no detectable stenosis, 1–49% stenosis, 50–99% stenosis, and complete occlusion (100%).

The outcomes of SCVDs were dichotomized as follows: lacunar infarction = presence (≥ 1 lesion) or absence, PVH = presence (Fazekas grade ≥ 2) or absence, DSWMH = presence (Fazekas grade ≥ 3) or absence, microbleeds = presence (≥ 1 microbleed) or absence, and ICAS = presence (≥ 1% stenosis) or absence.

To investigate the association of BP indexes with the overall total burden of small vessel disease (SVD), we created a "total SVD score" composed of four MRI outcomes: lacunar infarction, microbleeds, PVH, and DSWMH [2, 24]. The presence of each outcome was awarded 1 point using the dichotomization criteria described above, and the sum of the outcomes made the total score of the SVD burden with a minimum score of 0 (no outcome) and a maximum of 4 (all outcomes).

Statistical Analysis

Continuous and categorical variables were expressed as the mean ± standard deviation (SD) and a number (percentage) or percentage only, respectively. To compare demographic and clinical characteristics between Visits 1 and 2, *P* values were shown for continuous variables using the paired *t*-test and categorical variables using paired proportions (McNemar's test). In Visits 1 and 2, a logistic regression analysis was performed to assess the relationship between 1-SD higher of each BP index and the presence of a single MRI or MRA outcome.

To adjust for concurrent potential confounders, we adjusted for the following covariates in the multivariable logistic model: age, BMI, HbA1c, LDL-C, HDL-C, smoking status, drinking status,

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Table 1. Demographic and clinical characteristics of 616 men in Visit 1 [2006-2008] (aged 40-80) and Visit 2 [2010-2014] (aged 46-83); Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA), Shiga, Japan

Characteristics	Visit 1	Visit 2	*P* value*
Age, years	63.6 ± 9.2	68.2 ± 8.1	< 0.001
BMI, kg/m^2	23.5 ± 2.8	23.3 ± 2.8	< 0.001
Office blood pressure, mmHg			
SBP	135.6 ± 17.9	132.1 ± 16.9	< 0.001
DBP	80.2 ± 10.7	77.4 ± 10.4	< 0.001
PP	55.4 ± 12.4	54.8 ± 12.5	0.141
MAP	98.6 ± 12.2	95.6 ± 11.5	< 0.001
Home blood pressure, mmHg			
SBP	135.4 ± 17.1	134.8 ± 16.6	0.363
DBP	80.6 ± 10.4	78.1 ± 10.2	< 0.001
PP	54.8 ± 12.0	56.7 ± 12.4	< 0.001
MAP	98.9 ± 11.7	97.0 ± 11.3	< 0.001
LDL-C, mg/dL	126.5 ± 31.5	119.3 ± 31.7	< 0.001
HDL-C, mg/dL	60.0 ± 17.3	60.0 ± 16.7	0.957
HbA1c (%), NGSP	5.74	5.93	< 0.001
Medication			
Hypertension, *n* (%)	173 (28.1)	226 (36.7)	< 0.001
Diabetes mellitus, *n* (%)	57 (9.3)	88 (14.3)	< 0.001
Dyslipidemia, *n* (%)	88 (14.3)	130 (21.1)	< 0.001
Smoking status, *n* (%)			< 0.001
Current	175 (28.4)	116 (18.8)	
Past	326 (52.9)	385 (62.5)	
Never	115 (18.7)	115 (18.7)	
Drinking status, *n* (%)			0.249
Current	491 (79.7)	501 (81.3)	
Past	30 (4.9)	25 (4.1)	
Never	95 (15.4)	90 (14.6)	

Values are presented as mean ± standard deviation unless indicated otherwise

**P* value for continuous variables using paired *t*-test, and categorical variables using paired comparing proportions (McNemar's test)

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure; LDL-C (calculated by Friedewald equation), low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; HbA1c, hemoglobin A1c; NGSP, National Glycohemoglobin Standardization Program

hypertension medication, diabetes mellitus medication, and dyslipidemia medication. The results of the model were presented as odds ratio (OR) and 95% confidence interval (CI). In addition, these analyses were all repeated using home BP indexes. A sensitivity analysis that excluded participants receiving hypertension medication was performed.

Since age is a critical risk factor for developing SCVDs, we tested the interaction between office BP indexes and age in the multivariable logistic regression model. Furthermore, we performed multivariable logistic regression after stratifying participants by age into two groups of less than 65 years and greater or equal to 65 years.

To assess the relationship of 1-SD increment of office BP indexes and the total SVD score, we used univariable (unadjusted model) and multivariable (adjusted model) ordinal logistic regression. The adjusted covariates are the same in the multivariable logistic model. Results were presented as OR with 95% CI. Two-sided *P* values were presented for all analyses, and the significance of differences was set at $P<0.05$. All analyses were performed on SAS software, version 9.4 (SAS Institute, Cary, NC).

Results

The demographic and clinical characteristics of participants are shown in Table 1. Among the 616 eligible participants in this study, mean age ± SD was 63.6 ± 9.2 years at Visit 1 and 68.2 ± 8.1 years at Visit 2. At Visit 1, office SBP (135.6 ± 17.9 mm Hg), DBP

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Table 2. Frequency of subclinical cerebrovascular disease assessed by MRI of 616 men at MRI visit [2012-2015] (aged 45-84)

Brain MRI outcomes	*n* (%)
Lacunar infarction	121 (19.6)
Periventricular hyperintensity	146 (23.7)
Deep subcortical white matter hyperintensity	130 (21.1)
Microbleeds	78 (12.7)
Intracranial artery stenosis	172 (27.9)

Values are presented as number (percentage)
MRI, magnetic resonance imaging

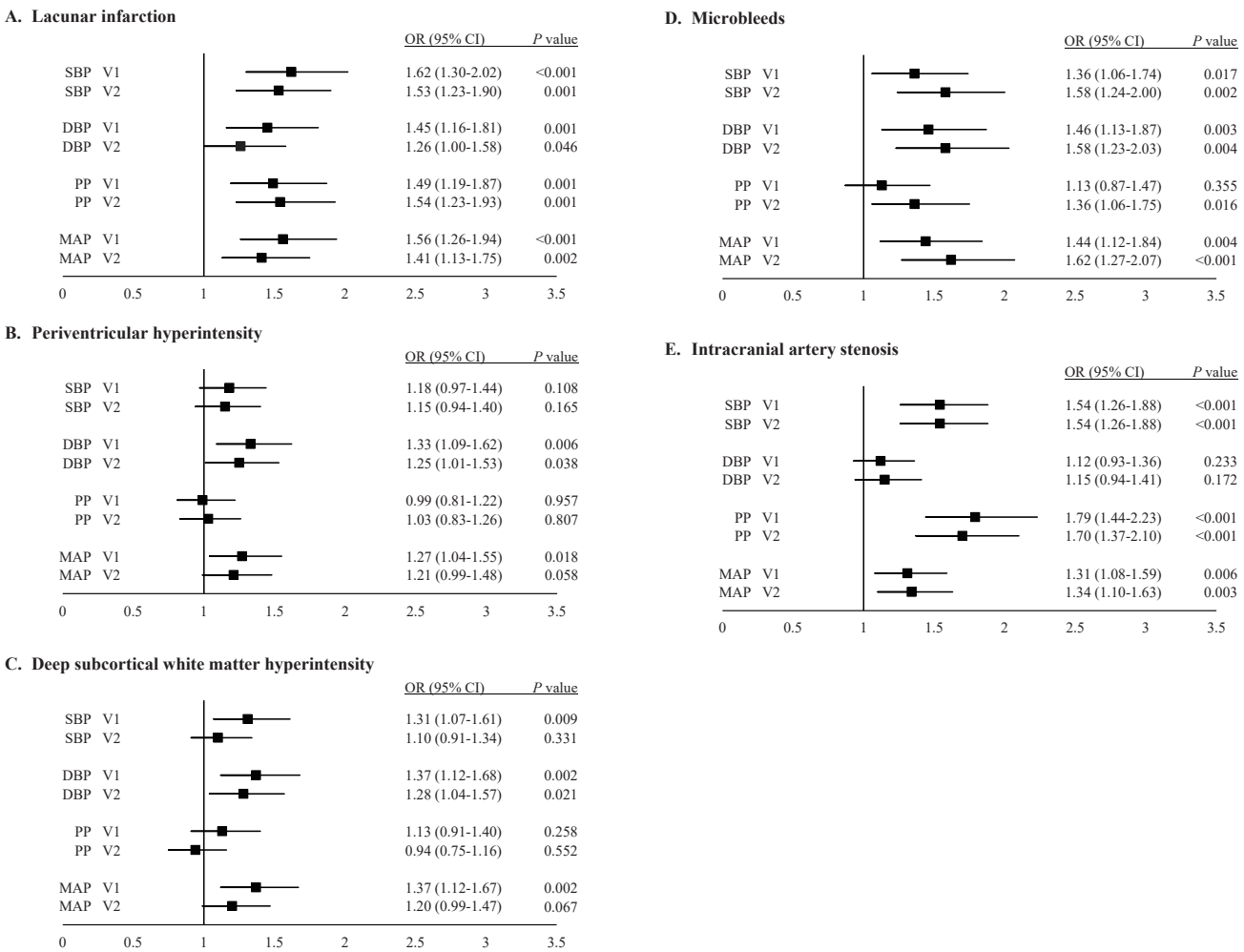

Fig. 1. Multivariable adjusted odds ratio for the presence of MRI outcomes per 1-SD higher office BP indexes of 616 men in Visits 1 (aged 40–80) and 2 (aged 46–83)

The variables adjusted in the multivariable model in Visits 1 and 2 are age, BMI, HbA1c, LDL-C, HDL-C, smoking status, drinking status, hypertension medication, diabetes mellitus medication, and dyslipidemia medication. V1, Visit 1; V2, Visit 2; OR, odds ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure

(80.2 ± 10.7 mm Hg), and MAP (98.6 ± 12.2 mm Hg) were significantly higher than at Visit 2, whereas PP at Visit 1 (55.4 ± 12.4 mm Hg) was only slightly higher. Home PP was significantly higher at Visit 2 than at Visit 1. Participants at Visit 2 had lower LDL-C levels and higher HbA1c levels and were past

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smokers and current drinkers. The percentage of participants receiving hypertension medication was higher at Visit 2 than at Visit 1 (36.7% vs. 28.1%). The frequencies of SCVDs detected using neuroimaging scans were lacunar infarction (19.6%), PVH (23.7%), DSWMH (21.1%), microbleeds (12.7%), and ICAS (27.9%) **(Table 2)**. A total of 90 (14.6%) participants had both PVH and DSWMH.

Fig. 1 shows multivariable adjusted OR for the presence of MRI outcomes per 1-SD higher of each office BP index (SBP, DBP, PP, and MAP) at Visits 1 and 2. SBP at Visit 1 associated with lacunar infarction, DSWMH, microbleeds, and ICAS, and that at Visit 2 associated with lacunar infarction, microbleeds, and ICAS. DBP at Visits 1 and 2 associated with lacunar infarction, PVH, and DSWMH, with a slightly higher OR at Visit 2 than at Visit 1 for microbleeds [OR; 1.46 (Visit 1) vs. 1.58 (Visit 2)]. Visit 1 and 2 PP associated with lacunar infarction and ICAS, while only Visit 2 PP associated with microbleeds [OR 1.13; 0.87–1.47 (Visit 1) vs. 1.36; 1.06–1.75 (Visit 2)]. Visit 1 MAP associated with all SCVDs, whereas Visit 2 MAP seems to not associate with white matter lesions (PVH and DSWMH) [OR; (PVH) 1.21; 0.99–1.48 and (DSWMH) 1.20; 0.99–1.47]. To summarize, lacunar infarction associated with SBP, DBP, PP, and MAP at both visits; PVH and DSWMH associated with DBP at both visits; microbleeds appear to show stronger association with the four BP indexes at Visit 2; and ICAS associated with SBP, PP, and MAP at both visits.

After testing the interaction between office BP indexes at each visit and age in the multivariable regression model, we found no interaction ($P>0.05$) except for Visit 2 DBP ($P=0.012$) and MAP ($P=0.041$) in ICAS (data not shown). The number of participants in each group after age stratification was 333 for less than 65 years and 283 for greater or equal to 65 years. In the age-stratified analysis in multivariable logistic regression, we found that the association of office BP indexes and MRI outcomes in each age group was less significant due to lower statistical power compared to pre-age stratification analysis (data not shown).

A sensitivity analysis that excluded participants receiving hypertension medication at each visit was performed **(Supplemental Fig. 1)**. Most of the associations observed before the exclusion of these participants seem to remain significant after the exclusion ($P<0.05$), except for lacunar infarction at Visit 2 for SBP, DBP, and MAP, PVH and DSWMH at Visit 2 for DBP, and DSWMH for SBP at Visit 1, which showed no significance after the exclusion. Additional analysis using home BP indexes appear to show similar relationships to those using office BP indexes at both visits; however, differences were observed in some relationships **(Supplemental Fig. 2)**.

We looked into the association of office BP indexes with a total SVD score. **Supplemental Table 1** shows the number and percentage of participants for each SVD score. Most participants had no SVD outcome ($n=346$; 56.2%), whereas 15 (2.4%) had them all, and 137 (22.3%) had one SVD outcome. **Supplemental Table 2** shows the univariable and multivariable ordinal logistic regression for the relationship of 1-SD higher office BP indexes and the total SVD score. Using the total score, the association of office BP indexes remains significant in almost all the indexes in both univariable and multivariable models, except for Visit 2 DBP in the univariable model and Visit 1 PP in the multivariable model. The effect of office BP indexes on the score seems fairly similar at both visits for each BP index in the multivariable model.

Discussion

In this study, we examined the associations of four office BP indexes measured at two different visits and SCVDs detected by MRI in general Japanese men. The results obtained showed SBP, PP, and MAP at both visits associated with lacunar infarction, microbleeds, and ICAS, while DBP at both visits associated with all SCVDs, except ICAS. All four BP indexes at Visit 2 showed slightly stronger association with microbleeds than those at Visit 1.

Only few studies have investigated the relationships between various BP indexes and different types of brain MRI and MRA outcomes in one study population. A study on European women reported relationships between DBP and MAP and the presence and severity of white matter lesions, but not for SBP or PP[9], while a study by the Northern Manhattan Study Group found a relationship between DBP and lacunar lesions, presumably ischemic and white matter hyperintensity volumes, but not SBP[11]. These findings are consistent with our results on white matter lesions (PVH and DSWMH); however, the present results also revealed a relationship between SBP and DSWMH at Visit 1. In previous studies, a strong relationship was observed between PP and white matter lesions[8, 9]; however, PP in this study was not associated with white matter lesions at Visits 1 and 2 or microbleeds at Visit 1. Only few observational studies found relationship between BP and microbleeds in general Asian populations, including Japan, and even fewer in Western populations[25]. This discrepancy may be attributed to differences in genetic and

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environmental backgrounds among populations that may create distinct microbleed characteristics[26]. However, a previous cross-sectional study showed that BP levels independently associated with the presence of microbleeds in a hypertensive population in the Netherlands[25].

This study is the first to show relationships between BP indexes from two different periods and subclinical ICAS in a general population. A previous study by Park *et al.* on symptomatic ICAS patients from the cilostazol trial in four East Asian countries showed that high SBP (≥ 160 mm Hg) in recent ICAS stroke patients during a 7-month period was strongly associated with the progression of symptomatic ICAS[27]. The Asymptomatic Polyvascular Abnormalities in Community (APAC) study group in China demonstrated that high SBP, MAP, and PP were associated with asymptomatic ICAS and also that PP was the strongest predictive value (area under the curve = 0.737)[28]. In this study, we confirmed that Visit 1 and 2 SBP, PP, and MAP associated with ICAS and that PP was strongly associated, especially Visit 1 PP.

Few studies have investigated the relationship between BP and SCVDs using BP measured from two different periods within the same study population. Four studies, one by Ohasama[29] and three Western studies[8, 9, 11], examined this relationship longitudinally over a period of more than 5 years, and the findings obtained were consistent with the present results showing relationships among SBP, DBP, and MAP and white matter lesions, but not PP. Similar results were obtained for ICAS at both visits, which is consistent with the findings from a cross-sectional APAC study on PP showing the strongest relationship with ICAS[28]. Although the present results agree with the findings of previous studies, these studies examined relationships at one time point, whereas we used two (Visits 1 and 2). We attempted to clarify the relationship between BP indexes measured at each time point and the probability of SCVDs through specific pathophysiological mechanisms.

To obtain a more detailed understanding of the pathophysiological mechanisms underlying these relationships, two factors need to be considered: the relationships between different BP indexes and MRI outcomes, and the period at which BP indexes were measured before the outcome. Differences in these relationships underlie distinct pathophysiological pathways. In relation to lacunar infarction, PVH, and DSWMH, increases in SBP and DBP cause mechanical stress, which damages the vasculature and alters cerebrovascular autoregulation, leading to endothelial dysfunction, vessel wall thickening, microatheroma, and atherosclerotic diseases. The progression of this pathway is gradual and could vary in time to the onset of the outcome, depending on several factors like age and the use of medication. This may explain the stronger relationship between BP indexes measured at Visit 1 for these outcomes if the early stages of the outcome initiated before Visit 1[14, 15, 30, 31]. Another plausible explanation is the possibility that the outcome happened immediately after Visit 1, which could have affected the relationship and undermined the strength of association at Visit 2. In contrast, microbleeds pathway is more instantaneous and appeared to be more strongly associated with recent increase in BP indexes, at Visit 2, which may result in wall tension and inflammation in small arterioles, causing weakened and damaged vessel walls, micro-aneurysms, and vessel rupturing[14, 32]. The mechanism causing ICAS is major arteries being affected by changes in SBP and PP, which stretch and relax the arteries, disrupting their elastic composition. As a result of decreases in the elasticity of arteries, vessel walls become stiffer and the perfusion capacity in diastole degrades, which increases PP[27, 28].

Recent studies investigated the burden of total SVD as a better measure to capture the combined effect of these outcomes on the brain than individual outcomes as they often occur simultaneously. A paper by Yang *et al.*[33] explored the relationship between 24-h ambulatory BP levels and variability and the total burden of SVD identified by brain atrophy, lacunae, PVH, DSWMH, microbleeds, and enlarged perivascular space. They showed significant associations between SBP level and SBP variability with the total SVD score, but neither with DBP levels nor DBP variability. In this study, we found an accumulation of the SVD burden with each 1-SD increment in almost all BP indexes, even after adjusting for conventional cerebrovascular risk factors. Since these outcomes are correlated, they share similar pathogeneses. To the best of our knowledge, this is the first study to assess the relationship of different BP indexes and the total SVD score in the general population.

Age is an important risk factor in developing SCVDs. We tested the interaction term between office BP indexes and age in the multivariable logistic regression model and found no interaction in almost all of office BP indexes except for Visit 2 DBP and MAP in ICAS. After stratifying the participants into two age groups of less than 65 and greater or equal to 65, we found the associations of 1-SD higher office BP indexes and MRI outcomes in the multivariable logistic regression to be weaker with lower statistical power. This might be due to the decrease of sample

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size in each age group leading to lower number of events for each outcome.

It is generally accepted that older people tend to have higher BP. In our study, although the participants at Visit 2 were 5 years older than at Visit 1, Visit 2 BP indexes were lower than those at Visit 1 **(Table 1)**. This seems to be due to an increased percentage of participants under hypertension medication at Visit 2 than at Visit 1 (36.7% vs. 28.1%).

We used office and home BP to investigate the relationships between BP indexes and SCVDs, and similar results were obtained. The Ohasama study examined the relationships between ambulatory, home, and clinic BP and SCVDs[29] and identified ambulatory and home BP, but not office BP, as significant predictors of SCVDs. However, the present results revealed similar relationships of office and home BP indexes to SCVDs, with differences in the strength of the association. Home BP indexes show weaker association to the SCVDs, especially at Visit 2. A possible explanation for this is that the participants with high BP during Visit 1 were encouraged to modify their lifestyle, which might explain the decrease of BP values at Visit 2 than at Visit 1 and the weaker association at Visit 2 for office and home BP with the exception of microbleeds. Another possible explanation is the time difference of the BP measurement between the office and home BP, since the office BP was measured between 9:00 and 11:00 in the morning, while home BP was measured in earlier hours within 1 h of waking up after urination, before breakfast, or taking any medications. We previously reported that accurately measured office BP with strict 5-min rest at silent office strongly correlated with home BP ($r=0.74$, $P<0.001$), and similar relationships were observed between the accurately measured office and home BP and coronary artery calcification (systolic home BP P heterogeneity vs. office BP $=0.813$)[12]. We concluded that accurately measured office BP is a reliable estimate; however, clinicians need to prioritize the use of home BP when available. Therefore, clinicians need to carefully assess and separately evaluate four BP indexes, specifically measured at home, as a tool for the early prevention of potential stroke. This needs to be considered in addition to the existence of conventional cerebrovascular risk factors, such as hypertension, diabetes mellitus, dyslipidemia, and smoking.

This study had several strengths. Our BP indexes were examined at two different periods (Visits 1 and 2), and both office and home measurements were collected, making it possible to examine the association between BP indexes and the MRI outcomes using both BP measurements. ICAS was included as MRI outcome, in which so far few reports exist on ICAS. However, this study has some limitations. First, MRI outcomes were not collected at baseline (Visit 1); therefore, we cannot know the exact time of the onset of SCVDs during the follow-up, and the progression of MRI outcomes cannot be examined. There is also a possibility that we assessed the reproducibility of the association of BP indexes at Visits 1 and 2 with MRI outcomes. Second, the results obtained were from Japanese men only; therefore, difficulties are associated with generalizing these results to females and non-Japanese populations. Finally, in the MRI visit, there were no measurements or collection of clinical characteristics, such as BP or hypertension medication data, and hence, the results obtained may be influenced by potential confounding factors.

Conclusion

In general Japanese men, BP indexes were associated with most brain MRI outcomes, and BP indexes measured at two visits associated with different MRI-assessed SCVDs. Deliberate evaluation of each BP index separately, in addition to conventional cerebrovascular risk factors, may be used as a tool for early prevention of potential stroke.

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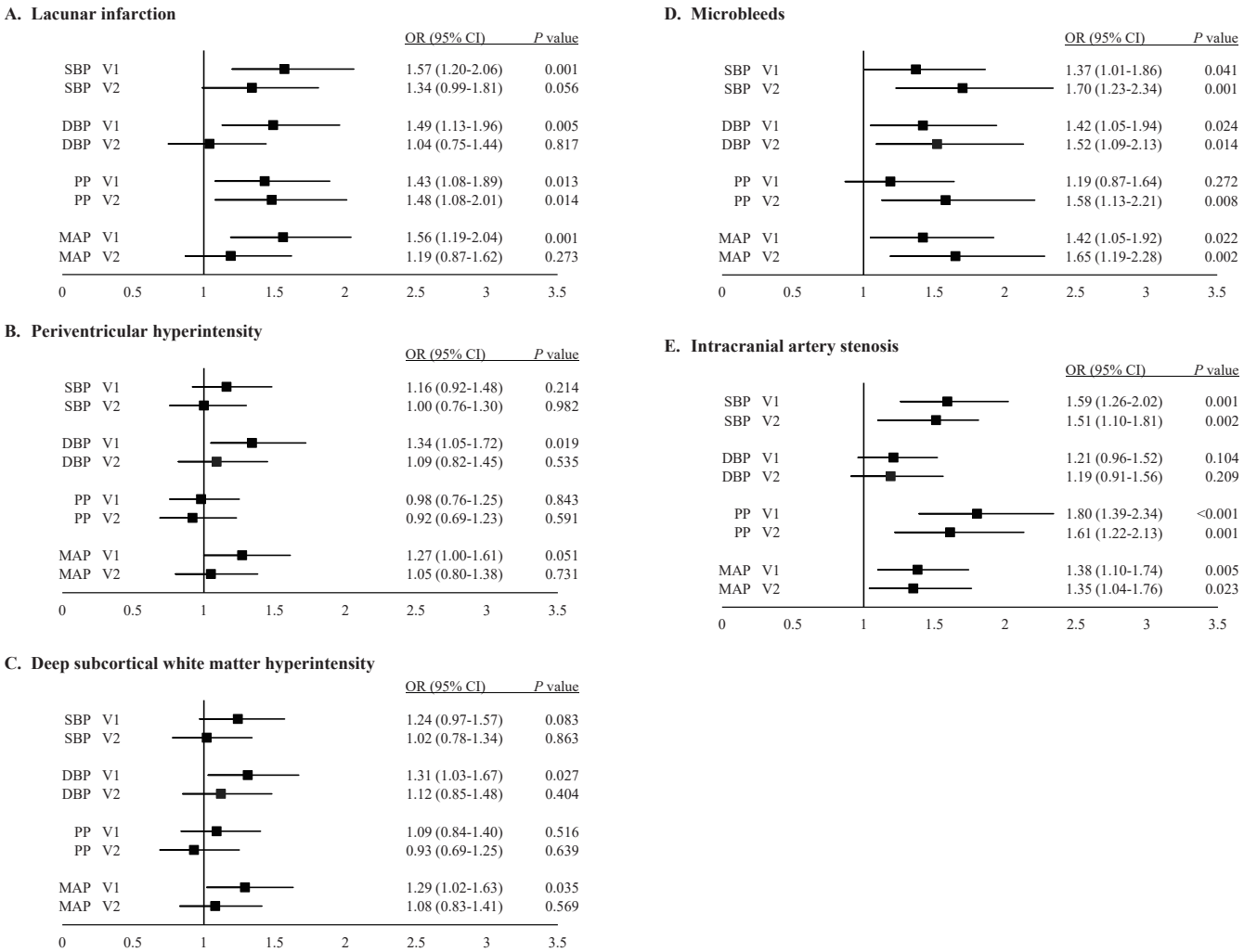

Supplemental Fig. 1. Sensitivity analysis of adjusted odds ratio for the presence of MRI outcomes per 1-SD higher office BP indexes in Visits 1 [V1 = 443] (aged 40–80) and 2 [V2 = 390] (aged 46–83) after the exclusion of participants receiving hypertension medication

The variables adjusted in the multivariable model in Visits 1 and 2 are age, BMI, HbA1c, LDL-C, HDL-C, smoking status, drinking status, diabetes mellitus medication, and dyslipidemia medication. V1, Visit 1; V2, Visit 2; OR, odds ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure

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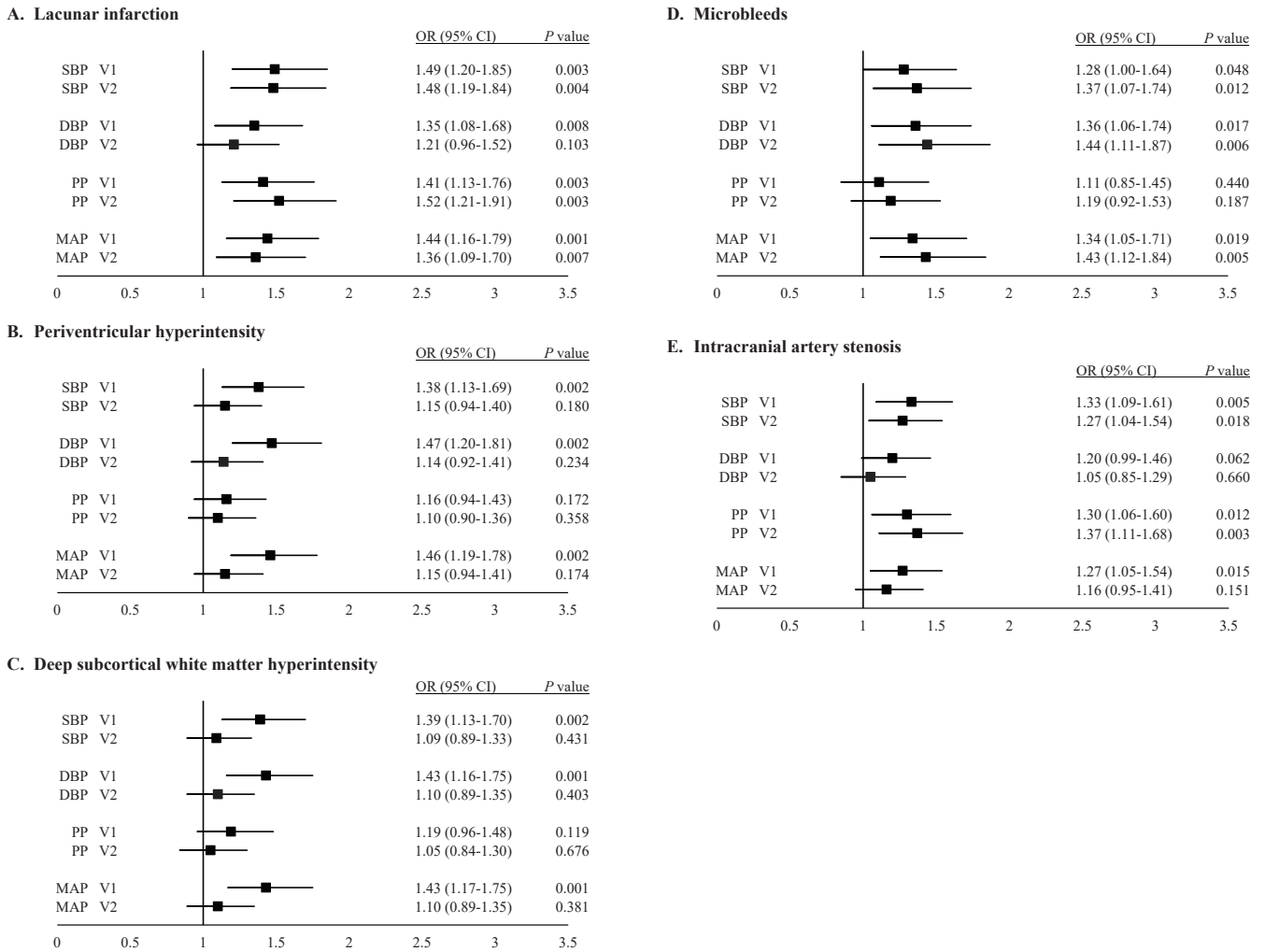

Supplemental Fig. 2. Multivariable adjusted odds ratio for the presence of MRI outcomes per 1-SD higher home BP indexes of 616 men in Visits 1 (aged 40–80) and 2 (aged 46–83)

The variables adjusted in the multivariable model in Visits 1 and 2 are age, BMI, HbA1c, LDL-C, HDL-C, smoking status, drinking status, hypertension medication, diabetes mellitus medication, and dyslipidemia medication. V1, Visit 1; V2, Visit 2; OR, odds ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure

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Supplemental Table 1. Frequency of participants in each score value of the total small vessel disease score (*N*=616)

SVD Score	*n* (%)
0	346 (56.2)
1	137 (22.3)
2	76 (12.3)
3	42 (6.8)
4	15 (2.4)

Values are presented as number (percentage)
SVD, small vessel disease

Supplemental Table 2. Univariable and multivariable ordinal logistic regression for the relationship of 1-SD office BP indexes and total small vessel disease score (*N*=616)

			Total SVD score	
			Univariable model	Multivariable model
SBP	V1	OR (95% CI)	1.52 (1.30 - 1.78)	1.34 (1.13 - 1.57)
		P value	<0.001	0.001
	V2	OR (95% CI)	1.44 (1.23 - 1.67)	1.33 (1.13 - 1.56)
		P value	<0.001	0.001
DBP	V1	OR (95% CI)	1.32 (1.14 - 1.54)	1.41 (1.19 - 1.66)
		P value	0.001	<0.001
	V2	OR (95% CI)	1.11 (0.95 - 1.29)	1.34 (1.13 - 1.58)
		P value	0.177	0.001
PP	V1	OR (95% CI)	1.42 (1.22 - 1.65)	1.14 (0.96 - 1.35)
		P value	<0.001	0.142
	V2	OR (95% CI)	1.48 (1.27 - 1.72)	1.20 (1.01 - 1.42)
		P value	<0.001	0.038
MAP	V1	OR (95% CI)	1.45 (1.24 - 1.69)	1.40 (1.19 - 1.65)
		P value	<0.001	<0.001
	V2	OR (95% CI)	1.27 (1.09 - 1.48)	1.36 (1.16 - 1.60)
		P value	0.002	0.001

The variables adjusted in the multivariable model in Visit 1 and Visit 2 are age, BMI, HbA1c, LDL-C, HDL-C, smoking status, drinking status, hypertension medication, diabetes mellitus medication, and dyslipidemia medication.
SVD, small vessel disease; V1, Visit 1; V2, Visit 2; OR, odds ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure

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