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【 ORIGINAL ARTICLE 】

# Total Small Vessel Disease Score in Neurologically Healthy Japanese Adults in the Kashima Scan Study

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**Abstract:**

**Objective** We explored the association between the total small vessel disease (SVD) score obtained with magnetic resonance imaging and risk factors and outcomes in the Japanese population.

**Methods** The presence of SVD features, including lacunes, cerebral microbleeds, white matter changes, and basal ganglia perivascular spaces on MRI, was summed to obtain a "total SVD score" (range 0-4). Ordinal and multinomial logistic regression analyses were performed to investigate the association of higher total SVD scores with vascular risk factors, the Mini-Mental State Examination (MMSE) score, and cerebral atrophy.

**Results** We included 1,451 neurologically healthy adults (mean age, 57.1 years; 47% male). A multivariate ordinal logistic regression analysis showed that the total SVD score was associated with aging, hypertension, blood pressure (BP), diabetes mellitus, MMSE score, and deep cerebral atrophy, but the equal slopes assumption between scores did not hold. A multivariate multinomial logistic regression analysis (total SVD score 0= reference) showed that aging, hypertension, and BP were positively associated with scores of 1, 2, or ≥3. These effects, presented as odds ratios (ORs), increased as the score increased and were strongest with a score of ≥3 [aging (per 10-year increment), OR 4.00, 95% confidence interval (CI) 2.47-6.46; hypertension, OR 5.68, 95% CI 2.52-12.80; systolic BP (per standard deviation increase), OR 1.96, 95% CI 1.41-2.74, respectively]. Diabetes mellitus and deep cerebral atrophy tended to be associated with the SVD scores. The MMSE score showed no consistent associations.

**Conclusion** The total SVD score may be a promising tool for indexing SVD, even in the Japanese population.

**Key words:** cerebral small vessel disease, hypertension, diabetes mellitus, cerebral atrophy, cognitive impairment

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## Introduction

Sporadic cerebral small vessel disease (SVD) is one of the most frequent age-related pathological processes in the brain and plays a crucial role in stroke and dementia (1). Effective prevention of SVD-associated brain injury requires a better understanding of its underlying causes and mechanisms, including early asymptomatic stages in healthy elderly individuals. Small vessels cannot currently be directly

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visualized *in vivo*, but associated cerebral parenchymal lesions on magnetic resonance imaging (MRI) are useful as biomarkers of SVD (1-3).

SVD markers often co-exist and are related to each other. In the Kashima Scan Study, we previously showed that lacunes, severe periventricular hyperintensity (PVH) or white matter hyperintensity (WMH), and severe basal ganglia (BG) or centrum semiovale perivascular spaces (PVSs) were significantly associated with cerebral microbleeds (CMBs) (4). These SVD markers on MRI have been investigated separately, and associations with vascular risk factors, including hypertension, stroke, and dementia, have been demonstrated.

Recently, the concept of a total SVD score, comprising four major MRI markers of SVD [i.e., lacunes, CMBs, severe PVH or WMH, and severe PVS in the BG (BG-PVS)] has been proposed as a comprehensive index of SVD severity in the brain (5). This score has been validated in stroke patient cohort studies and a healthy population study of a Caucasian (Scottish) group involved in the development of this score (5-7). However, the prevalence of each underlying SVD pathology appears to differ slightly between Asian and Caucasian populations: For example, confluent WMH is more frequently seen in Asian populations than in Caucasian populations (8), and cerebral amyloid angiopathy (CAA)-related intracerebral hemorrhage appears to be more frequent in Caucasian populations than in Asian populations (9).

The aim of this study was to investigate the presence of valid associations between an elevated total SVD score and the prevalence of vascular risk factors, global cognitive status, and the degree of cerebral atrophy in a neurologically healthy Japanese cohort.

## Materials and Methods

### Subjects

Subjects were evaluated as part of a cross-sectional analysis (i.e., using baseline data at entry) of the Kashima Scan Study, an ongoing population-based cohort study investigating age-related brain changes on MRI (10, 11). A total of 1,739 consecutive adults who underwent health screening tests of the brain including brain MRI at our center at their own expense between December 2005 and November 2011 were considered for this study. The inclusion criteria were as follows: age ≥20 years, no disability in instrumental activities of daily living, ability to independently visit our center for current health screening tests of the brain, and provision of written informed consent. The exclusion criteria were as follows: inability to undergo brain MRI, a history of any neurological disorder or brain injury, and abnormalities detected during the neurological examination.

### Standard protocol approvals, registrations, and participant consent

All protocols were approved by the institutional review board of the Saga University Faculty of Medicine (Saga, Japan) and Yuai-Kai Oda Hospital (Kashima, Japan). Written informed consent was obtained from all participants.

### Baseline assessment

All subjects were examined by a general physician and a certified neurological surgeon. We recorded the clinical characteristics, including the age, sex, smoking status, history of ischemic heart disease, duration of education, actual blood pressure (BP) values [including systolic BP, diastolic BP, pulse pressure, and mean arterial pressure = (systolic BP-diastolic BP)/3+diastolic BP], presence of hypertension, diabetes mellitus, and dyslipidemia. Actual systolic and diastolic BPs were measured in the morning with the patient in a sitting position using a standard mercury sphygmomanometer. Hypertension was defined as systolic BP >140 mmHg and/or diastolic BP >90 mmHg or the use of antihypertensive medication. Diabetes mellitus was defined as a fasting serum glucose level ≥126 mg/dL and/or hemoglobin A1c levels ≥6.5% and/or the use of anti-diabetic medications. Dyslipidemia was defined as fasting serum low-density lipoprotein cholesterol ≥140 mg/dL and/or triglyceride ≥150 mg/dL and/or high-density lipoprotein cholesterol ≤40 mg/dL and/or the use of anti-dyslipidemic agents. Subjects who were smokers at the time of enrolment were classified as current smokers. The history of ischemic heart disease was obtained from each subject. The duration of education was also obtained from each subject and ranged from 6 to 18 years. The global cognitive function was assessed using the Mini-Mental State Examination (MMSE) (12), which was administered by a skilled nurse or physician (93% and 7% of subjects, respectively). A total MMSE score <27 was defined as impaired (13, 14).

### Brain MRI acquisition and analyses

Brain MRI was performed using a 1.5-Tesla scanner (EXCELART Vantage, version 7.0; Toshiba Medical Systems, Tokyo, Japan). The parameters of axial MRI (T1-weighted imaging, T2-weighted imaging, fluid-attenuated inversion recovery, and gradient-echo T2*-weighted MRI) are described in the supplementary methods section (please see Supplementary material 1). There were no changes in the MRI protocol or settings during the study period.

All raters of MRI findings were blinded to the clinical data. The components of the total SVD score, including lacunes (of presumed vascular origin), CMBs, WMH and PVH (both of presumed vascular origin), and BG-PVS, were classified according to the international consensus definition of the standard criteria for reporting vascular changes on neuroimaging (3). The details of the ratings criteria, as well as the values for inter- and intra-rater reliability for the SVD markers, are described in the supplementary methods section (please see Supplementary material 1). Briefly, the inter- and intra-rater reliability values for MRI findings ranged from 0.45-0.71 and 0.66-0.87, respectively.

Using a semiautomatic method with a computer-assisted

processing system (Image J version 1.41; National Institutes of Health, Bethesda, USA), the percent cerebrum value was calculated as an index of cerebral atrophy (15, 16). The degree of ventricular enlargement (an index of deep cerebral atrophy) and of subdural space enlargement (an index of cortical atrophy) were also determined. Formulas for each index of atrophy are described in the supplementary methods section (please see Supplementary material 1).

### Determining the total SVD score and classification for analyses

According to the recently developed scoring system (5-7), scores were assigned as follows: the presence of lacunes or CMBs was defined as the presence of one or more foci (1 point if present, respectively); the presence of moderate to severe PVH or WMH was defined as either irregular PVH extending into the deep white matter (Fazekas score 3) and/or (early) confluent deep WMH (Fazekas score 2 or 3) (17) (1 point if present); and the presence of moderate to severe BG-PVS was counted if it was grade 2-4 (1 point if present: details of PVS grading are described in Supplementary material 1). Thus, the total SVD score ranged from 0 to 4. In the analyses, subjects with a total SVD score of 3 or 4 were combined, as these 2 subgroups were small (n=24, 1.65% and n=13, 0.89% of the total subjects examined, respectively). We therefore compared 4 groups of subjects: those with a total SVD score of 0, 1, 2, and ≥3 points.

### Statistical analyses

The statistical analyses were performed using the IBM SPSS statistics software program, version 21.0 (IBM, Armonk, USA). Univariate analyses for comparison of the four groups were performed using the $\chi^2$ test and analysis of variance, as appropriate. Age, hypertension, and diabetes mellitus were selected as potential confounders for the total SVD score, because a common type of SVD (type 1 SVD: age-related and vascular risk factor-related SVD) is strongly associated with these factors (1). Thus, each multivariate analysis was performed after adjusting for these confounders as well as for sex. The BP was adjusted for only age, sex, and diabetes mellitus, due to the strong association between BP and hypertension. As a primary analysis to investigate the associations of these factors with the total SVD score, a multivariate ordinal logistic regression analysis and a multivariate multinomial logistic regression analysis were performed. For the sensitivity analysis, an analysis of covariance (ANCOVA) of the continuous variables that showed significance in the multivariate multinomial logistic regression analysis was performed after adjusting for the potential confounders, as described above. In each univariate analysis or multivariate logistic regression analysis, p values <0.05 were considered statistically significant. With the multivariate ordinal logistic regression analysis, the equal slope assumption of the effect of variables with a significant ordinal trend was also assessed: p values ≥0.05 suggest that the equal slopes assumption holds, which means that the effect of independent variables [i.e., odds ratio (OR)] is equal between scores adjacent to each other, indicating a meaningful ordinal logistic regression analysis.

The study was performed and reported with reference to the guidelines in Strengthening the Reporting of Observational Studies in Epidemiology (18).

## Results

Of the potentially eligible subjects (n=1,739), 217 declined to enroll, 1 could not undergo MRI because of claustrophobia, and 13 had a history of a neurological disorder or brain injury with abnormalities seen on MRI. Among the remaining 1,508 subjects, 8 with MRI that displayed motion artifacts, 1 with numerous cavernous angiomas, and 48 with incomplete data for the analysis were excluded. Thus, our final sample included 1,451 subjects (675 men; median age, 57.1 years; range, 22-84 years).

The details of the characteristics of the entire cohort, as well as the number of subjects with each total SVD score, are shown in Table 1. The majority of the subjects scored 0 (71.9%), and the remaining subjects (28.1%) scored ≥1 point. In univariate analyses of the four groups, we found significant differences in the prevalence of all variables except current smoking status and dyslipidemia. The prevalence of hypertension, diabetes mellitus, dyslipidemia, and a low education level appeared to be associated with a consistently higher total SVD score. Older age, higher BP values, ventricular and subdural space enlargement, and cerebral atrophy were also consistently associated with a higher total SVD score. Fig. 1A shows the prevalence of lacunes, CMBs, moderate to severe PVH or WMH, and moderate to severe BG-PVS in each total SVD score group (detailed data are also shown in Supplementary material 2). In each group with a score of 1, 2, or ≥3, punctate foci in the cerebral parenchyma such as lacunes and CMBs were present at low frequencies compared to widespread lesions, such as a substantial degree of PVH/WMH and BG-PVS. The prevalence of subjects with a score ≥1 increased with age, and we observed a significant difference in the SVD score according to age ($p<0.001$, $\chi^2$ test: Fig. 1B).

The results of the multivariate ordinal logistic regression analysis for relevance to a higher total SVD score are shown in Table 2. Age, sex, smoking status, hypertension, BP, diabetes mellitus, MMSE score, cerebral atrophy, and the degree of ventricular enlargement (an index of deep cerebral atrophy) were relevant to the total SVD score. However, the p values for the test of parallel lines of those variables were less than 0.05, suggesting that the equal slopes assumption did not hold.

The results of the multivariate multinomial logistic regression analysis for relevance to the total SVD score are shown in Table 3. The key results of this analysis are summarized in Fig. 2. Compared to a score of 0 (reference: OR =1.0), age, hypertension, and BP were significantly associated with a total SVD score of 1, 2, and ≥3, respectively. The pres-

**Table 1. Clinical and Imaging Findings in All Subjects and Each Total SVD Score with Univariate Comparison.**

| Variables | All (n=1,451) | Score 0 (n=1,043: 71.9%) | Score 1 (n=290: 20.0%) | Score 2 (n=81: 5.6%) | Score ≥3 (n=37: 2.5%) | p value |
|---|---|---|---|---|---|---|
| Age, mean (SD), years | 57.1 (9.7) | 55.6 (9.5) | 59.7 (9.6) | 63.5 (7.8) | 66.5 (6.9) | <0.001 |
| Sex, male, n (%) | 675 (46.5) | 461 (44.2) | 150 (51.7) | 41 (50.6) | 23 (62.2) | 0.022 |
| Current smoker, n (%) | 239 (16.5) | 162 (15.5) | 57 (19.7) | 14 (17.3) | 6 (16.2) | 0.416 |
| Ischemic heart disease, n (%) | 28 (1.9) | 12 (1.2) | 8 (2.8) | 6 (7.4) | 2 (5.4) | <0.001 |
| Hypertension, n (%) | 502 (34.6) | 283 (27.1) | 136 (46.9) | 54 (66.7) | 29 (78.4) | <0.001 |
| Systolic BP, mean (SD), mmHg | 125.1 (17.9) | 122.5 (17.2) | 129.4 (18.2) | 136.2 (18.6) | 138.8 (12.3) | <0.001 |
| Diastolic BP, mean (SD), mmHg | 76.7 (11.0) | 75.4 (10.7) | 79.3 (11.4) | 81.8 (11.1) | 82.5 (9.9) | <0.001 |
| Pulse pressure, mean (SD), mmHg | 48.4 (12.5) | 47.2 (11.9) | 50.1 (13.2) | 54.4 (14.1) | 56.2 (11.8) | <0.001 |
| Mean arterial pressure, mean (SD), mmHg | 92.8 (12.4) | 91.1 (12.0) | 96.0 (12.6) | 100.0 (12.3) | 101.3 (9.2) | <0.001 |
| Diabetes mellitus, n (%) | 139 (9.6) | 80 (7.7) | 31 (10.7) | 18 (22.2) | 10 (27.0) | <0.001 |
| Dyslipidemia, n (%) | 785 (54.1) | 555 (53.2) | 156 (53.8) | 49 (60.5) | 25 (67.6) | 0.223 |
| Education, mean (SD), years | 12.4 (2.4) | 12.6 (2.3) | 12.3 (2.4) | 11.5 (2.6) | 11.0 (2.4) | <0.001 |
| MMSE score, mean (SD) | 29.53 (1.25) | 29.62 (1.09) | 29.32 (1.57) | 29.37 (1.62) | 29.03 (1.52) | <0.001 |
| MMSE score <27, n (%) | 79 (5.4) | 41 (3.9) | 28 (9.7) | 6 (7.4) | 4 (10.8) | 0.001 |
| Cerebral atrophy, mean (SD), % | 84.20 (4.25) | 84.73 (4.05) | 83.16 (4.52) | 82.50 (3.86) | 80.98 (4.62) | <0.001 |
| Ventricular enlargement, mean (SD), % | 8.28 (2.82) | 7.88 (2.66) | 9.05 (3.00) | 9.67 (2.61) | 10.53 (3.22) | <0.001 |
| Subdural space enlargement, mean (SD), % | 7.52 (2.36) | 7.39 (2.31) | 7.79 (2.52) | 7.83 (2.64) | 8.48 (2.18) | 0.002 |

BP: blood pressure, MMSE: Mini-Mental State Examination, SD: standard deviation

Continuous variables are presented as the mean (SD). Categorical variables are presented as number of subjects (%).

Univariate analyses were performed using the $\chi^2$ test for categorical variables and the analysis of variance for continuous variables.

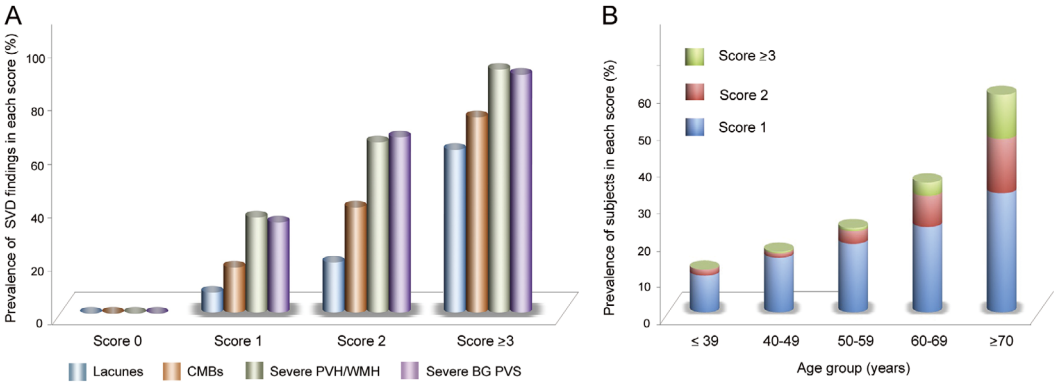


**Figure 1. Prevalence of SVD findings contributing to each total SVD score, and the total SVD score by age group. (A) The graph shows the prevalence of each SVD finding for each total SVD score. Blue represents subjects with lacunes, orange represents subjects with CMBs, green represents subjects with moderate to severe PVH or WMH (including subjects with PVH grade 3 and/or WMH grade 2 or more), and purple represents subjects with moderate to severe BG-PVS. (B) The graph shows the prevalence of each total SVD score by age group (p<0.001, $\chi^2$ test). Blue represents subjects with a score of 1, red represents subjects with a score of 2, and green represents subjects with a score of ≥3. BG: basal ganglia, CMBs: cerebral microbleeds, PVH: periventricular hyperintensity, PVS: perivascular spaces, SVD: small vessel disease, WMH: white matter hyperintensity**

ence of diabetes mellitus was associated with a score of 2 and ≥3. These effects, presented as ORs, increased as the SVD score increased. A decrease in the MMSE score and the prevalence of subjects with MMSE <27 were significantly associated with a score of 1, but we found no marked difference between a score of 0 and a score of 2 or ≥3. We found a significant association with the degree of ventricular enlargement and a score of 1, as well as a trend toward an association with a score of 2 and ≥3.

As a sensitivity analysis, an ANCOVA of the continuous variables found to be significant in the multivariate multinomial logistic regression analysis was performed (Supplementary material 3 and Supplementary material 4). All variables (age, BP, and degree of ventricular enlargement) were found to be significantly higher in subjects with a total SVD score of 1, 2, or ≥3 than in those with a score of 0. Regarding age, subjects with a score of 2 or ≥3 were significantly older than those with a score of 1. The systolic BP and the arterial pressure were significantly higher in subjects with a total SVD score of 2 than in those with a score of 1. No vari-

**Table 2. Multivariate Ordinal Logistic Regression Analysis for Relevance to a Higher Total SVD Score.**

| Variables | OR (95% CI) | p value for test of parallel line* |
|---|---|---|
| Age (per 10 years) [a] | 1.78 (1.55-2.05) | 0.007 |
| Sex, male [b] | 1.29 (1.01-1.65) | 0.007 |
| Current smoker [c] | 1.46 (1.45-2.06) | 0.017 |
| Ischemic heart disease [c] | 1.90 (0.93-3.88) | - |
| Hypertension [d] | 2.47 (1.93-3.15) | 0.007 |
| Systolic BP (per SD=17.9 mmHg) [d] | 1.48 (1.31-1.68) | 0.011 |
| Diastolic BP (per SD=11.0 mmHg) [d] | 1.50 (1.33-1.71) | 0.013 |
| Pulse pressure (per SD=12.5 mmHg) [d] | 1.22 (1.09-1.38) | 0.018 |
| Mean arterial pressure (per SD=12.4 mmHg) [d] | 1.55 (1.37-1.76) | 0.010 |
| Diabetes mellitus [c] | 1.59 (1.11-2.28) | 0.007 |
| Dyslipidemia [c] | 1.04 (0.82-1.32) | - |
| Education (per year) [c] | 0.97 (0.92-1.02) | - |
| MMSE score [c] | 0.93 (0.85-1.01) | - |
| MMSE score <27 [c] | 1.66 (1.05-2.62) | 0.006 |
| Cerebral atrophy (per SD=4.25%) [c] | 0.87 (0.75-0.99) | 0.013 |
| Ventricular enlargement (per SD=2.82%) [c] | 1.29 (1.13-1.47) | 0.017 |
| Subdural space enlargement (per SD=2.36%) [c] | 0.95 (0.84-1.08) | - |

BP: blood pressure, CI: confidence interval, MMSE: Mini-Mental State Examination, OR: odds ratio, SD: standard deviation, SVD: small vessel disease

* p value for test of parallel line is presented for variable with significant ordinal trend.

[a]adjusted for sex, hypertension, and diabetes mellitus; [b]adjusted for age, hypertension, and diabetes mellitus; [c]adjusted for age, sex, hypertension, and diabetes mellitus; [d]adjusted for age, sex, and diabetes mellitus.

**Table 3. Multivariate Multinomial Logistic Regression Analysis of Clinical and Cerebral Atrophy Findings Relevant to Each Total SVD Score (score 0=reference).**

| Variables | Score 1 (n=290: 20.0%) | Score 2 (n=81: 5.6%) | Score ≥3 (n=37: 2.5%) |
|---|---|---|---|
| | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| Age (per 10 years) [a] | 1.51 (1.30-1.76) | 2.38 (1.75-3.23) | 4.00 (2.47-6.46) |
| Sex, male [b] | 1.32 (1.01-1.74) | 1.10 (0.68-1.78) | 1.69 (0.83-3.46) |
| Current smoker [c] | 1.46 (1.00-2.14) | 1.55 (0.78-3.10) | 1.38 (0.51-3.77) |
| Ischemic heart disease [c] | 1.61 (0.63-4.06) | 3.01 (1.04-8.70) | 1.87 (0.38-9.31) |
| Hypertension [d] | 1.92 (1.45-2.54) | 3.67 (2.23-6.04) | 5.68 (2.52-12.80) |
| Systolic BP (per SD=17.9 mmHg) [d] | 1.35 (1.18-1.56) | 1.83 (1.46-2.31) | 2.00 (1.44-2.78) |
| Diastolic BP (per SD=11.0 mmHg) [d] | 1.39 (1.21-1.60) | 1.90 (1.47-2.45) | 2.04 (1.40-2.97) |
| Pulse pressure (per SD=12.5 mmHg) [d] | 1.15 (1.00-1.32) | 1.36 (1.09-1.69) | 1.42 (1.05-1.93) |
| Mean arterial pressure (per SD=12.4 mmHg) [d] | 1.41 (1.22-1.62) | 1.97 (1.54-2.54) | 2.19 (1.51-3.17) |
| Diabetes mellitus [e] | 1.08 (0.69-1.70) | 2.43 (1.32-4.47) | 2.75 (1.21-6.26) |
| Dyslipidemia [c] | 0.93 (0.71-1.22) | 1.18 (0.73-1.92) | 1.71 (0.82-3.57) |
| Education (per year) [c] | 1.00 (0.94-1.07) | 0.94 (0.84-1.04) | 0.89 (0.77-1.03) |
| MMSE score [c] | 0.90 (0.82-0.99) | 0.98 (0.83-1.17) | 0.91 (0.73-1.12) |
| MMSE score<27 [c] | 2.13 (1.27-3.56) | 1.25 (0.50-3.17) | 1.71 (0.54-5.39) |
| Cerebral atrophy (per SD=4.25%) [c] | 0.86 (0.73-1.00) | 0.93 (0.71-1.22) | 0.83 (0.57-1.20) |
| Ventricular enlargement (per SD=2.82%) [c] | 1.28 (1.10-1.49) | 1.28 (0.99-1.65) | 1.37 (0.96-1.96) |
| Subdural space enlargement (per SD=2.36%) [c] | 0.98 (0.84-1.13) | 0.86 (0.67-1.10) | 0.94 (0.67-1.33) |

BP: blood pressure, MMSE: Mini-Mental State Examination, OR: odds ratio, CI: confidence interval, SD: standard deviation, SVD: small vessel disease

ORs (95% CI) are results of multivariate multinomial logistic regression analysis (Score 0=reference): [a]adjusted for sex, hypertension, and diabetes mellitus; [b]adjusted for age, hypertension, and diabetes mellitus; [c]adjusted for age, sex, hypertension, and diabetes mellitus; [d]adjusted for age, sex, and diabetes mellitus; [e]adjusted for age, sex, and hypertension.

ables were significantly different when comparing subjects with a score of 2 versus ≥3.

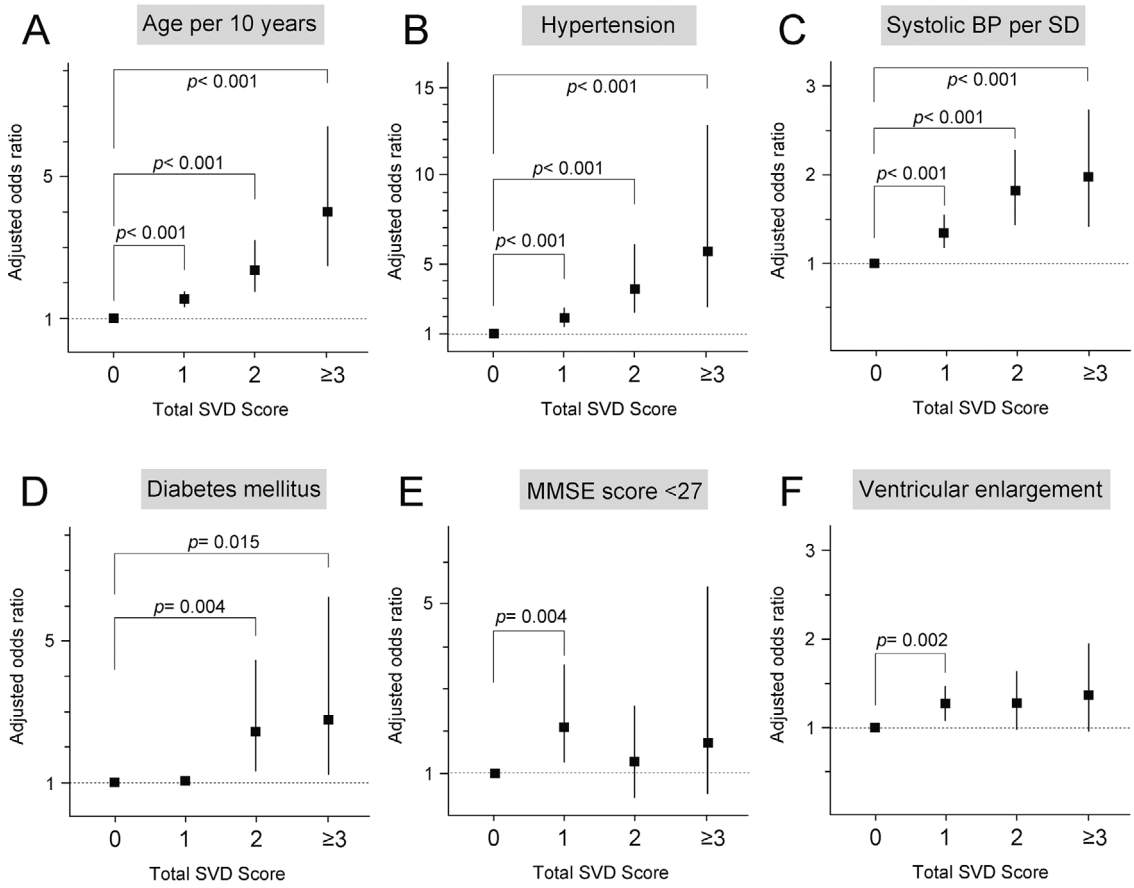


**Figure 2.** **Representative graphs of the results of a multinomial logistic regression analysis. The graphs show odds ratios (squares), 95% confidence intervals (bars), and p values. BP: blood pressure, MMSE: Mini-Mental State Examination, SD: standard deviation, SVD: small vessel disease (A) adjusted for sex, hypertension, and diabetes mellitus; (B) and (C) adjusted for age, sex, and diabetes mellitus; (D) adjusted for age, sex, and hypertension; (E) and (F) adjusted for age, sex, hypertension, and diabetes mellitus.**

## Discussion

The associations of the total SVD score in neurologically healthy populations have been examined in Caucasian cohorts (population-based cohort, or hypertensive subjects cohort) (7, 19). The main result of our study is that the total SVD score first evaluated in a neurologically healthy Asian (Japanese) cohort also had some associations with cerebrovascular risk factors (age, high BPs, and diabetes mellitus) and deep cerebral atrophy. However, we should note that our primary analyses showed that the effect of those variables on higher total SVD scores appeared to be inconsistent. These results suggest that the difference in pathological severity between scores was not be equal and may be due to the different weights for a point with each SVD finding.

The prevalence of each total SVD score (0, 1, 2, and ≥3) in our healthy cohort (71.9%, 20.0%, 5.6%, and 2.6%, respectively) was similar to that in a healthy Caucasian (Spanish) healthy cohort (71.8%, 19.7%, 6.8%, 1.7%, respectively) (19) but seemed to be different from the prevalence in another Caucasian (Scottish) study: low scores (0-2) were present in fewer healthy Scottish individuals in this cohort (44.4%, 36.6%, 14.4%, and 4.6%) (7). This difference may have been caused by the higher age range of subjects, higher prevalence of cardiovascular diseases (including ischemic heart disease), or higher systolic BP in the healthy Scottish cohort than in the healthy Spanish or Japanese cohort. Determining the actual reasons for this difference will require further investigation (i.e., international collaborating study). High scores (≥3) were frequently seen in stroke patient cohorts (39%, 24%, 19%, 14%, and 4%) (6), suggesting that, as expected, the severity of SVD appeared to be lower in our healthy cohort than in stroke cohorts.

In this study, the prevalence of hypertension, as well as all BP values (especially systolic BP and mean arterial pressure) increased as the total SVD score increased. SVD includes type 1 pathology [arteriosclerosis (age and hypertension-related)], type 2 pathology (cerebral amyloid angiopathy), and others (types 3-6) (1). No pathological data were available for this cohort, so we were unable to conclude which type of SVD pathology was reflected by the total SVD score. However, our finding of a consistent associa-

tion between vascular risk factors (i.e., age, hypertension, BP) and total SVD score may imply that the total SVD score reflects the severity of "type 1 class" SVD. An association between comprehensive SVD burden and chronic kidney disease (19, 20), both of which share vascular risk factors (including age and hypertension), might support this hypothesis.

Independent associations between different BP components and the risk of a cardiovascular event or death have been reported (21, 22). However, which BP component has the greatest predictive ability for such events remains controversial (22). Although few previous studies have simultaneously investigated the association between BP components and individual SVD markers, diastolic BP appears to be a key component for SVD (23-25). In our study, the systolic BP and mean arterial pressure had the strongest association with the order of total SVD scores, a finding that conflicts with those of previous reports. Our adoption of a different approach to evaluating SVD makers may explain this discrepancy; the presence of individual SVD markers was evaluated in previous studies, whereas the severity of the comprehensive SVD burden was observed in this study. However, to clarify this issue, further investigations, including ambulatory BP monitoring, will be needed.

In this study, anatomically widespread-type SVD lesions (i.e., presence of moderate to severe PVH/WMH or BG-PVS) were more frequent (40-42% with a score of 1) and further developed, even in the early stage, than punctate focus-type SVD lesions (i.e., presence of lacunes or CMBs, 9-10% with a score of 1), findings that agree with those of a previous study (6). Why the development process differed so markedly among SVD markers is unclear, but these results suggest that blood-brain barrier (BBB) dysfunction first leads to BBB permeability (26), as well as leakage of fluid and blood products into the vessel wall and perivascular space (5). This may suggest that white matter changes and enlarged perivascular spaces are eligible markers of early-stage BBB dysfunction.

A previous study showed that the total SVD score was associated with superficial atrophy (6), conflicting with our finding of a trend toward an association between deep cerebral atrophy and the total SVD score. These differences may be due in part to the different study samples and atrophy assessment methods used. SVD-related cerebral atrophy is accelerated with older age and high BP among patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (27). A volumetric MRI study demonstrated a significant association between hypertension and lateral ventricular enlargement (28).

We did not observe an association between the total SVD score and global cognitive function. As described below, determination of the global cognitive function with MMSE showed relatively low sensitivity and may have contributed to the absence of an association. However, a recent cross-sectional study also demonstrated no clear association between the total SVD score and cognitive decline in community-dwelling elderly subjects (7). To focus on the prevention of SVD-related vascular cognitive impairment, further exploration is needed.

The strengths of our study include the prospective design, standardized imaging, and the large number of neurologically healthy participants. However, our study has several limitations as well. First, the potential for selection bias could not be excluded, as our subjects sought brain health screening tests at their own expense, potentially introducing a bias toward individuals who were relatively affluent or who had high concern regarding their own health; this may reflect differences in educational background and socioeconomic status, which are important factors in cardiovascular disease (29). Second, we were unable to pathologically confirm the type and severity of SVD or certain vascular risk factors, such as atrial fibrillation, carotid plaques, or retinopathy. Third, the global cognitive function was determined using the MMSE, which although widely used, has relatively low sensitivity for the assessment of the cognitive function in patients with SVD (30). Therefore, we cannot conclude that an association is present between SVD scoring and cognition. Fourth, although the indexes of cerebral atrophy were measured semi-automatically with a validated computer-assisted processing system, only a single slice was used for this procedure. Furthermore, subjects with neurological disorders were excluded by self-report and/or neurological examinations. Because we did not use volumetric MRI or single photon emission computed tomography to evaluate specific focal degeneration of the brain, several subjects with potential neurodegenerative disease might have been included. Finally, due to the cross-sectional nature of this study, we could not determine the prognostic significance of the total SVD score.

In conclusion, even in a neurologically healthy Japanese cohort, the total SVD score was correlated with major vascular risk factors (including hypertension, and all components of BP values) and showed a trend toward an association with deep cerebral atrophy, providing additional construct validity for this scoring concept. The total SVD score might be a promising tool for indexing SVD worldwide, especially regarding hypertensive nature.

**The authors state that they have no Conflict of Interest (COI).**

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