Middle-age cerebral small vessel disease and cognitive function in later life: a population-based prospective cohort study

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Summary

Background Cerebral small vessel disease (cSVD) is a major pathologic substrate of vascular contribution to cognitive impairment. However, population based long-term longitudinal cognitive function data in relation to cSVD are rare. We investigated the relationship between cSVD and cognitive decline over time in middle-aged through elderly population.

Methods This prospective cohort study was conducted in a community-based adult population (avg. age 58.5 ± 6.4) who underwent both magnetic resonance imaging (MRI) and comprehensive neuropsychological tests at baseline (2011–2014). The participants were followed-up with the same neuropsychological test battery 4-yearly in two more cycles (in 2015–2018 and 2019–2022). A total of 2454 participants who were free of dementia and cerebrovascular disease at baseline with cognitive function testing at least 2 time points over the time were analyzed. Data analysis was performed from May 1, 2023 to January 31, 2024. SVD was defined by the presence of any of the visible MRI markers (age-related white matter change, lacunes and cerebral microbleeds) at baseline. The main outcomes were multivariable adjusted mean differences of cognitive test performances by cSVD groups over time. The neuropsychological assessment battery included verbal and visual memory, verbal fluency, Digit Symbol–coding, Trail Making Test–A, and Stroop Test. To examine the relationship between cSVD and cognitive function, we used linear mixed model for repeated measurements to compare the means (95% CIs) by cSVD groups.

Findings Of the total, 908 (37.0%) participants had cSVD on MRI reading at baseline. By location, cSVD were mostly found in the frontal lobe followed by basal ganglia area of the brain. None of the cognitive test scores, except Trail Making Test–A, were significantly different between the cSVD groups at baseline. At 8-year follow-up, participants without cSVD performed significantly better than participants with cSVD in Stroop–color reading [Mean difference 1.19 (95% CI: 0.02–2.36), p = 0.0451] and visual reproduction-recognition [Mean difference 0.11 (95% CI: 0.01–0.21), p = 0.0221]. While no other cognitive tests showed any differential changes by cSVD groups, logical memory (Story Recall Tests) increased and Stroop-word reading decreased over time in both cSVD groups almost identically.

Interpretation Silent cSVD was independently associated with decline in executive functioning over 8-year follow-up period in this Korean middle-aged through elderly general population. Future studies considering wider spectrum of cSVD and longer follow-up durations may help predict further cognitive outcomes.

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Keywords: Cerebral small vessel disease; Cognitive function; Dementia; Aging population

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Research in context

Evidence before this study

We searched PubMed with the MeSH search terms "cerebral small vessel disease*", and "cognitive dysfunction*", with Boolean operator 'AND'. We set study publishing date from Jan 01, 1994 to December 31, 2023 and filtered title and abstract in English language for the search terms. We further selected the population based studies only. One hundred and seventeen studies were initially identified that investigated the relationship between cerebral small vessel disease (cSVD) and cognitive function with 27 studies involving relatively healthy subjects (Supplementary Fig. S2); some reported in relation to total cSVD burden (i.e., White matter hyperintensities, brain infarct, cerebral microbleeds etc. combined), while others reported with individual components of cSVD. However, most studies have investigated the relationship between cSVD and cognitive function cross-sectionally. While there are few longitudinal studies have been reported, most are from elderly population of Caucasian origin.

Added value of this study

To the best of our knowledge, this is one of the very few studies to examine longitudinal relationship between cSVD and cognitive function among Asian populations (Supplementary Table S6), expanding the knowledge base from previous studies investigating cSVD associated cognitive decline. Due to the insidious nature of cognitive decline, especially in the middle-aged, it is important to follow up for a longer duration to observe the natural course. From a large population-based Korean cohort, we report 8-year trajectory of cognitive function in relation to baseline cSVD, where participants with cSVD exhibited lower executive functioning compared to the participants without cSVD at the end the follow-up period. Repeated cognitive testing may have reduced the sensitivity to longitudinal decline in some of the cognitive function performances in our study, perhaps due to learning effect, however, the differential gains associated with cSVD especially in episodic memory, may provide valuable insights into the role of cSVD as a predictive marker of future cognitive decline.

Implications of all the available evidence

Our study suggests that presence of cSVD in the middle-age may be an independent risk factor of executive functioning decline in later life. This study, therefore, adds to the accumulating evidence emphasizing the need for prevention of cSVD earlier in the lifespan to optimize cognitive function in older ages and, hence, contribute to preventing dementia.

Introduction

Cerebral small vessel disease (cSVD) refers to all the pathological processes that affect the small vessels of the brain (arteries, arterioles, capillaries and small veins) and are found in the brain's white and deep grey matter.[1] The most common visible radiological markers of the disease include white matter hyperintensities (WMH) and lacunes of presumed vascular origin, cerebral microbleeds, visible perivascular spaces and cerebral micro-infarcts.[2,3] Although, majority of cSVD manifests sub-clinically,[4] it is a major source of cognitive impairment during aging process leading to mild cognitive impairment and dementia.[5] Cognitive dysfunction caused by cSVD may account for two-thirds of all vascular dementia (VaD).[6]

Although cSVD is associated with cognitive function, it is unclear whether middle-aged adults with cSVD who are neurologically healthy, would acquire faster cognitive decline over time compared to the non-CSVD counterpart.[7–10] Additionally, the natural course of cognitive decline in relation to cSVD in middle-aged through older adults lacks due to unavailability of large population based longitudinal data.[9,11] Very few population-based prospective studies have been done among the Asian populations, especially in middle-aged subjects.[12,13] From a relatively younger adults (avg. age of 59 years) of rural Chinese population-based prospective study, Jiang and colleagues reported that participants with cSVD markers had a steeper decline in Mini-Mental State Examination (MMSE) score and higher risk of incident all-cause dementia over a 5-year follow-up.[12] However, the relationship between cSVD markers and domain-specific longitudinal cognitive decline in the similar age group of general adult population remains unclear. Converging evidence suggests cSVD associated cognitive function decline, especially in processing speed and executive functioning.[6,9,11,14] However, these studies were conducted in elderly populations where disentanglement of specific etiology of cognitive dysfunctions might be difficult because of the onset of general age related cognitive decline.[9,15] Among adults 60 years and older, prevalent mild cognitive impairment (MCI) ranges from approximately 7%–25% and by the age 70, approximately two-thirds of the population may experience some form of cognitive impairment.[16,17] Hence, large prospective cohort studies involving middle aged general adult population is warranted to investigate the temporal relationship of cSVD and cognitive decline.

Here in this study, we aimed to analyze the 8- year trajectories of cognitive functions in relation to clinically silent cSVD in general middle-aged through elderly adults in the community using cognitive test battery.

Methods

Study participants

Participants of the current study were recruited as part of the Korean Genome and Epidemiology Study

(KoGES), a population-based study which started in 2001 in Ansan city of South Korea.[18] Magnetic Resonance Imaging (MRI) and neuropsychological test protocol was added to the KoGES core examinations as ancillary study on aging (KoGES-Ansan Aging Study) which was introduced in Exam 6 and Exam 7 (between years 2011 through 2014).[19,20] At baseline, a total of 2964 participants aged 49 to 79 underwent MRI examinations. Of the total, 2868 participants (after excluding participants a history of clinically symptomatic cerebrovascular disorders or reported to have diagnosed with dementia) were invited to perform neuropsychological test at baseline and 2-cycles of follow-ups in 2015–2018 and 2019–2022 respectively. Participants with incomplete (n = 58) or only once performed neuropsychological tests (n = 316) were further excluded. Finally, 2454 participants performing neuropsychological tests at least 2 times (a total 6648 assessments) with a mean follow-up of 7.91 (±1.54) years were included for analyses (Fig. 1). Signed informed consent was obtained from each participant, and the ethical approval of study procedures were granted by the institutional review board (IRB No. 2006AS0045) of the Korea University Ansan Hospital.

Neuropsychological testing

KoGES neuropsychological test battery consists of the tests that were applied to the participants of the Framingham Heart Study (FHS) Original and Offspring cohorts, and test procedures and methods were adapted from the FHS protocol.[21,22] Most of the neuropsychological tests were available in Korean versions, while some were adapted from the original tests from Wechsler Adult Intelligent Scale-Revised (WAIS-R) and Wechsler Memory Scale-III (WMS-III). The details of cognitive assessment are described in our prior publications and supplementary document (Supplementary Table S1).[23,24] Briefly, verbal memory was evaluated with Story Recall tests adapted from WMS-III. Verbal Fluency assessment consisted of phonemic tests from the Controlled Oral Word Association Test and categorical fluency containing animal naming. Visual memory was assessed with the Visual Reproduction (VR) tests from the WAIS-R. Digit Symbol coding test was performed for evaluation of visual processing and sustained attention according to the Wechsler Adult Intelligence Scale-fourth edition protocol. Simple attention was assessed by the Trail Making Test-A (TMA; number sequencing) and Stroop Test-Word

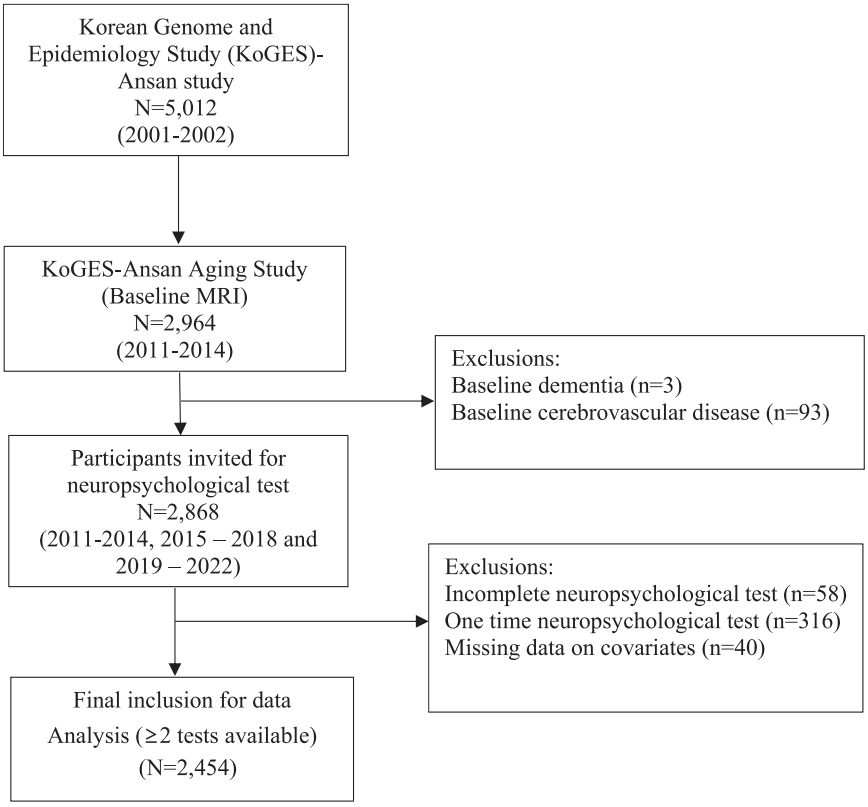

Fig. 1: **A flow chart illustrating the process for defining the study population.**

Reading. Executive functioning was measured with the Stroop Test-Color reading.[19] For all tests, except TMA, higher scores indicate better performance.

MRI data acquisition

Details of the MRI acquisition have been described in our previously published papers and supplementary document (Supplementary Fig. S1).[25,26] In short, all scans were performed on a GE Signa 1.5 T MR scanner (GE Medical Systems, Waukesha, WI, USA) with an 8-channel head coil. T2-weighted fluid-attenuated inversion recovery (FLAIR) images were used to evaluate the white matter in the brain. White matter changes (WMC) on MRI were identified when there were hyperintensities ≥5 mm on FLAIR images. The degree of WMC was scored using a four-point age-related white matter change (ARWMC)[27] scale (0 = no lesion, 1 = focal lesion of ≤10 mm, 2 = beginning confluent lesions, 3 = confluent lesions involving the entire region) in each right and left hemisphere in five different regions (frontal, parieto-occipital, temporal, basal ganglia, and infratentorial). The ARWMC total score was derived by summing the individual scores in each of the five regions, with the total score ranging between 0 to 30. Lacunes (of presumed vascular origin) are small subcortical infarcts of <15 mm in size in the region of the penetrating arteries in eight different regions (basal ganglia, frontal, thalamus, temporal, parietal, occipital, brainstem and cerebellum) following National Institute of Neurological Disorders and Stroke classification (NINDS, 1990). Microbleeds were defined as well-defined focal areas of low signal on T2*WI of <10 mm in diameter. We defined presence of SVD as the presence of any of the 3 visible radiological markers (ARWMC, lacune and cerebral microbleeds) that were available from MRI readings in our study. Assessment of severity/count of the lesions were not used for the current analysis because of low degrees of severity of lesions were observed among the study subjects (Supplementary Table S5). A trained radiologist who was blinded to the history and diagnosis of the participants scored all three radiological markers. An intrarater reliability was conducted across a 1-month interval with the data of 56 participants' ARWMC scoring, and the results indicated a high repeatability (Cronbach alpha = 0.96).[26]

Covariates

Covariates that could influence cSVD and cognition were measured at baseline. Questionnaires created for KoGES, were used to collect data on demographic information, lifestyle, health status and history of disease by specially trained examiners familiar with interview knowledge.[18] Self-reported regular exercise (exercise >30 min at least two times per week) data was collected. Alcohol drinking status (never, former, or current smoker) data was collected by asking participants whether they had ever consumed alcoholic beverages, whether there was a time in their life when they regularly consumed alcohol, and whether they drank alcohol in the past month. Self-reported smoking status (never, former, or current smoker) was also collected. Beck depression inventory (BDI), was used to assess the depressive symptoms scores.[28] Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Blood pressure has been measured as the average of the left and right arms using an appropriately sized cuff and a mercury sphygmomanometer (Baumanometer-Standby; W.A. Baum Co. Inc., New York, USA) and mercury-free blood pressure monitor (BPBIO210T, Inbody, Seoul, Korea) in a sitting position after resting for at least 5 min. Plasma concentrations of glucose, total cholesterol, triglycerides and high-density lipoprotein (HDL) cholesterol were measured enzymatically using a 747 Chemistry Analyser (Hitachi, Tokyo, Japan). Low-density lipoprotein (LDL) cholesterol levels were estimated using the Friedewald formula. Type 2 diabetes was defined as a fasting glucose concentration ⩾126 mg dL^{-1} or a post 2-h glucose after the 75-g OGTT ⩾200 mg dL^{-1}.[29] Additionally, participants who reported currently being under antidiabetic and/or antihypertensive medications were considered to have type 2 diabetes and/or hypertension. Medication history of lipid-lowering agents were also collected.

Statistical methods

All statistical analyses were performed with SAS software (9.4 version for Windows, Institute, Cary, NC, USA). Demographic, lifestyle, clinical, and other characteristics of study participants were expressed as the means (SDs) or numbers and percentages as per cSVD categories. One-way analysis of variance was done for continuous variables, and the χ^2 test was used for categorical variables. To examine the relationship between cSVD and cognitive function over time, we used linear mixed model for repeated measurements (restricted maximum likelihood method). We used unstructured covariance structure in the models to account for within-person correlation across time. The model performs an implicit missing data imputation assuming that data are Missing at Random (MAR). In our analyses, multivariable adjusted least squares means (95% confidence limits) of the cognitive function test scores of cSVD groups were calculated and compared to see if the mean differences (between participants without cSVD and participants with cSVD) were significant between the groups over time (at baseline and 1st and 2nd follow-ups at 4-year and 8-year respectively). Co-variate adjustments were made for age, sex, education levels (<middle school or ≥ graduating middle school), body mass index, total cholesterol, low density lipoprotein cholesterol, hypertension status, diabetes status and depressive symptoms score. An interaction term of cSVD with time was also included in the models. We performed sensitivity

analysis after excluding incident cerebrovascular disease (CEVD) cases since new CEVD events may play intermediary role in cognitive decline.[30,31] A two-tailed p value less than 0.05 was considered statistically significant for all analyses.

Role of the funder

The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Results

The general characteristics of the study participants are shown in Table 1. Of the total 2454 participants, 908 (37.0%) participants were found to have cSVD on MRI reading. Participants with cSVD were about 3 years older at baseline. Higher education level (graduating middle school or more) was proportionately lower in the participants with cSVD compared to the participants without cSVD group (n = 587; 64.65% vs. n = 1081; 69.92%, respectively). BMI, TG and HDL were not significantly different in the participants with cSVD compared to participants without cSVD. However, total cholesterol and LDL cholesterol were significantly lower in the participants with cSVD compared to the participants without cSVD group, perhaps, because of the higher proportional usage of lipid-lowering medication in the participants with cSVD (Table 1). Regular exercise and drinking status were not significantly different in the participants with cSVD compared to the participants without cSVD group. However, smoking status was significantly different in the participants with cSVD compared to the participants without cSVD group. Prevalent hypertension and diabetes were significantly higher in the participants with cSVD compared to the participants without cSVD group. History of CVD were also significantly higher in the participants with cSVD compared to the participants without cSVD group (n = 64; 7.05% vs. n = 62; 4.01% respectively).

Distribution of cSVD lesions

The prevalence of cSVD lesions and its distribution by location in brain are shown in Table 2. The prevalence of ARWMC is about 35.37% (n = 868). The prevalence of lacunes and microbleeds were 2.69% (n = 66) and 2.81% (n = 69) respectively. Among the various brain regions, ARWMC were most prevalent in the frontal and parieto-occipital region. Lacunes were higher in basal ganglia (1.47%; n = 36) and frontal area (0.81%; n = 20). Microbleed was higher in basal ganglia (0.73%; n = 18) and frontal area (0.57%; n = 14) as well. Overall, cSVD

General characteristics	Total (n = 2454)	Participants without cSVD (n = 1546)	Participants With cSVD (n = 908)
Age, years	58.53 (6.40)	57.22 (5.48)	60.74 (7.19)
Sex, Women	1226 (49.96)	771 (49.87)	455 (50.11)
Education, ≥middle school	1668 (67.97)	1081 (69.92)	587 (64.65)
BMI, kg/m^2	24.65 (2.97)	24.57 (2.92)	24.77 (3.03)
Total cholesterol, mg/dL	197.37 (35.66)	198.92 (35.14)	194.71 (36.37)
Triglyceride, mg/dL	132.58 (65.94)	132.0 (66.84)	133.54 (64.38)
HDL cholesterol, mg/dL	48.25 (12.24)	48.33 (12.23)	48.11 (12.26)
LDL cholesterol, mg/dL	122.6 (31.9)	124.19 (31.59)	119.89 (32.24)
Lipid-lowering medication user (n = 2185), yes	407 (18.63)	217 (15.77)	190 (23.49)
Regular exercise, yes	876 (35.70)	536 (34.67)	340 (37.44)
Smoking status			
Never	1478 (60.23)	933 (60.35)	545 (60.02)
Past	673 (27.42)	404 (26.13)	269 (29.63)
Current	303 (12.35)	209 (13.52)	94 (10.35)
Drinking status			
Never	1175 (47.88)	734 (47.48)	441 (48.57)
Past	134 (5.46)	80 (5.17)	54 (5.95)
Current	1145 (46.66)	732 (47.35)	413 (45.48)
BDI score[a]	6.0 (2.0–11.0)	6.0 (2.0–11.0)	6.0 (3.0–12.0)
Hypertension, yes	1063 (43.32)	574 (37.13)	489 (53.85)
Diabetes, yes	724 (29.50)	396 (25.61)	328 (36.12)
History of CVD, yes	126 (5.13)	62 (4.01)	64 (7.05)

[a]Median (interquartile range).

cSVD: cerebral small vessel disease; BMI: body mass index; HDL: High density lipoprotein; LDL: Low density lipoprotein; BDI: Beck depression inventory; CVD: Cardiovascular disease (includes history of myocardial infarction, coronary artery disease, angina pectoris, congestive heart failure, and arrhythmia). Values are presented as mean (SD) for continuous variables and n (%) for categorical variables, unless otherwise specified.

Table 1: **Baseline general characteristics of the study participants (N = 2454) by cerebral small vessel disease (cSVD) categories.**

	Left-hemisphere	Right-hemisphere	Total
ARWMC			868 (35.37%)
Frontal lobe	685 (27.91%)	684 (27.87%)	798 (32.52%)
Parieto-occipital lobe	316 (12.88%)	303 (12.35%)	369 (15.04%)
Temporal lobe	16 (0.65%)	16 (0.65%)	25 (1.02%)
Basal ganglia	27 (1.10%)	20 (0.81%)	35 (1.43%)
Infra-tentorial	3 (0.12%)	0	3 (0.12%)
Lacune (of presumed vascular origin)			66 (2.69%)
Frontal lobe	11 (0.45%)	13 (0.53%)	20 (0.81%)
Temporal lobe	3 (0.12%)	1 (0.04%)	3 (0.12%)
Parietal lobe	4 (0.16%)	2 (0.08%)	6 (0.24%)
Occipital lobe	2 (0.08%)	2 (0.08%)	4 (0.16%)
Basal ganglia	18 (0.73%)	26 (1.06%)	36 (1.47%)
Thalamus	3 (0.12%)	3 (0.12%)	4 (0.16%)
Infra-tentorial	4 (0.16%)	5 (0.20%)	8 (0.33%)
CMBs			69 (2.81%)
Frontal lobe	7 (0.29%)	7 (0.29%)	14 (0.57%)
Temporal lobe	7 (0.29%)	5 (0.20%)	12 (0.49%)
Parietal lobe	8 (0.33%)	6 (0.24%)	13 (0.53%)
Occipital lobe	3 (0.12%)	6 (0.24%)	9 (0.37%)
Basal ganglia	9 (0.37%)	12 (0.49%)	18 (0.73%)
Thalamus	7 (0.29%)	4 (0.16%)	10 (0.41%)
Infra-tentorial	6 (0.24%)	4 (0.16%)	8 (0.33%)

ARWMC: Age-related white matter change; CMBs: Cerebral microbleeds. Values are presented as n (%).

Table 2: **Shows distribution of cerebral small vessel disease (cSVD) lesions by location in brain (N = 2454).**

were mostly present in the frontal lobe followed by basal ganglia.

Changes in cognitive functions in relation to cSVD

The story recall tests (Logical Memory - immediate recall, delayed recall and recognition) scores were not significantly different between the cSVD groups at any time point (Table 3, Fig. 2), and the test scores increased significantly overtime in both the groups (Fig. 2.A.1, 2.A.2, 2.A.3). However, there was differential increase of visual reproductions test scores as opposed to story recall tests. Visual reproduction-recognition (VRR) test score increased only in participants without cSVD group, whereas, participants with cSVD group was stable over time resulting in a significant difference between the groups at 8-year time point [Mean difference 0.11 (0.01–0.21), p = 0.0221] (Fig. 2.B.3). Other visual reproduction tests (visual reproduction immediate and delayed recall) scores tended to show similar results to that of VRR at the 8-year period, but was not statistically significant (Fig. 2 and Table 3).

Non-significant differences were observed for verbal fluency (phonemic and category) test scores between the cSVD groups at baseline and during the follow-up times. Trail Making Test–A was significantly different between the cSVD groups at baseline, however, non-significant differences were observed during the follow-up times (Fig. 2D, Table 3). Non-significant differences were observed for digit symbol-coding test score between the cSVD groups at baseline and during the follow-up times.

We found that Stroop-color reading test score did not significantly differ at baseline [Mean difference 0.90 (–0.14 to 1.94), p = 0.0914] and 4-year follow-up [Mean difference –0.24 (–1.35 to 0.86), p = 0.6654]. However, at 8-year follow-up there was significantly better Stroop-color reading test score in the participants without cSVD group than the participants with cSVD [Mean difference 1.19 (0.02–2.36), p = 0.0451] (Fig. 2.F.2, Table 3). Stroop-word reading test scores were not significantly different between the cSVD groups at any time points, and it decreased over time in both groups in similar trajectories (Fig. 2.F.1, Table 3).

Sensitivity analysis

In the sensitivity analyses we excluded incident CEVD cases (n = 55) that occurred over the 8-year follow-up period. Similar results to that of without exclusions were observed in the sensitivity analyses. There was significantly better Stroop-color reading test score in the participants without cSVD group than the participants with cSVD [Mean difference 1.25 (0.07–2.43), p = 0.0370] (Supplementary Table S2). Also, compared to participants with cSVD, participants without cSVD group showed significantly better performance in all visual reproductions tests at 8-year follow-up (Supplementary Table S2). Another sensitivity analysis performed by excluding those with a history of contusion, head injury, CNS surgery/large vessel stroke and lobar intracerebral hemorrhages (n = 19) did not essentially change any results (Supplementary Table S3).

Discussion

In this large, population-based, prospective cohort study, participants with cSVD at baseline performed significantly worse than the participants without cSVD group on a couple of neuropsychological tests (i.e., Stroop-color reading and visual reproductions-recognition test) at 8-year follow-up. A shorter term (4-year) follow-up did not yield such significant worsening, indicating the effect of cSVD on cognitive functions may be insidious. On the other hand, however, logical memory functions (story recall tests-immediate, delayed and recognition) increased throughout the time period in both participants with cSVD and participants without cSVD almost identically; hinting to a possible learning effect due to repeated measurements. To the best of our knowledge, the findings are among the handful of previous studies to report significant association of clinically silent cSVD and various cognitive functions longitudinally over time in middle-aged (avg. age <60) through elderly Asian population at community level.

	Baseline		4-year		8-year	
	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
Story recall test						
Immediate recall	0.20 (−0.61 to 1.02)	0.6247	0.44 (−0.37 to 1.26)	0.2900	0.08 (−0.75 to 0.92)	0.8400
Delayed recall	0.09 (−0.73 to 0.93)	0.8155	0.28 (−0.58 to 1.15)	0.5261	0.21 (−0.67 to 1.09)	0.6401
Recognition	0.02 (−0.10 to 0.15)	0.7137	0.06 (−0.04 to 0.18)	0.2494	0.05 (−0.05 to 0.17)	0.3256
Visual reproductions						
Immediate recall	0.22 (−0.03 to 0.47)	0.0863	−0.21 (−0.46 to 0.04)	0.1006	0.25 (−0.001 to 0.51)	0.0518
Delayed recall	0.23 (−0.03 to 0.50)	0.0916	−0.29 (−0.57 to −0.01)	0.0386	0.25 (−0.02 to 0.53)	0.0714
Recognition	0.08 (−0.01 to 0.17)	0.0974	−0.03 (−0.13 to 0.06)	0.4911	0.11 (0.01–0.21)	0.0221
Verbal fluency						
Phonemic	0.78 (−0.08 to 1.64)	0.0774	−0.81 (−1.69 to 0.07)	0.0729	0.64 (−0.25 to 1.54)	0.1612
Category	0.16 (−0.17 to 0.51)	0.3464	0.001 (−0.34 to 0.34)	0.9920	0.11 (−0.24 to 0.46)	0.5333
Trails making						
Trails A–time	−1.50 (−2.85 to −0.14)	0.0299	−0.43 (−1.96 to 1.09)	0.5737	−1.30 (−2.90 to 0.29)	0.1088
Digit symbol						
Coding	1.17 (−0.35 to 2.70)	0.1321	−1.12 (−2.70 to 0.45)	0.1623	1.22 (−0.34 to 2.79)	0.1252
Stroop test						
Word reading	1.46 (−0.29 to 3.23)	0.1029	0.02 (−2.03 to 2.08)	0.9822	0.72 (−0.73 to 2.18)	0.3303
Color reading	0.90 (−0.14 to 1.94)	0.0914	−0.24 (−1.35 to 0.86)	0.6654	1.19 (0.02–2.36)	0.0451

[a]Adjusted for age, sex, education levels (<middle school or ≥ graduating middle school), body mass index, total cholesterol, low density lipoprotein cholesterol, hypertension status, diabetes status and depressive symptoms score.

Table 3: **Multivariable adjusted[a] mean difference (95% CI) of cognitive function test scores using linear mixed models for repeated measurements between the cSVD groups overtime (N = 2454).**

Few population-based prospective studies, although differed demographically from ours, reported similar cSVD related cognitive decline previously. In the Rotterdam study, Prins et al.,[9] found that structural brain changes caused by small-vessel disease, were specifically associated with decline in information processing speed and executive functioning. They reported that increasing severity of periventricular white matter lesions, brain atrophy and presence of brain infarcts were associated with steeper decline in performance on the Stroop test, the Letter–Digit Substitution Task and verbal fluency test. The study had a modest sample size with a population that are almost a decade older compared to our study sample. Additionally, after exclusion of participants with incident stroke, some of the associations of these lesions with measures of processing speed and executive function were no longer significant. In our study, the findings of associations of cSVD and Stroop-color reading and visual reproductions tests stayed significant even after exclusion of incident CEVD cases. The robustness of our findings is perhaps because of a relatively larger sample size and longer follow-up duration. Another study from the Lothian Birth Cohort, also reported cSVD's association with poorer processing speed.[32] However, the study was also conducted in a moderate number of elderly participants and the results may have been affected by overall general cognitive decline as reported in a separate investigation of the same study population.[33]

Our study findings supports the hypothesis that cSVD selectively impairs the executive functioning and not memory functions.[6,9,34] One possible mechanism underlying the relationship between cSVD and executive dysfunction may be linked to the location of most burden of lesions and its resultant cortical hypometabolism. For example, previous studies have reported that frontal hypometabolism may in fact be a result of strategically located infarcts which may damage frontal-subcortical networks,[35,36] thereby leading to reduced neuronal connectivity to the prefrontal cortex.[37–39] In our study, we observed WMH were most frequent in frontal lobe and for microbleeds and infarcts most frequently in the basal ganglia and frontal area (Table 2). However, it is also possible that Stroop test may be the most resilient test to memorizing, hence, practice effect might be least, thereby, eliciting an unbiased result.[40]

In our study, the logical memory (story recall) functions increased over time irrespective of presence or absence of cSVD. The observed increase may have happened due to the learning effect,[41] and as participants become more familiar with the test items, concepts and strategies with retesting.[42] Logical memory test of WMS is highly sensitive to learning effects as participants tend to remember the stimulus stories in subsequent re-assessments.[41,43] In our study, a short story with ''negative'' emotive details (where participants are asked to answer questions from a story of a child being kidnapped and following consequential

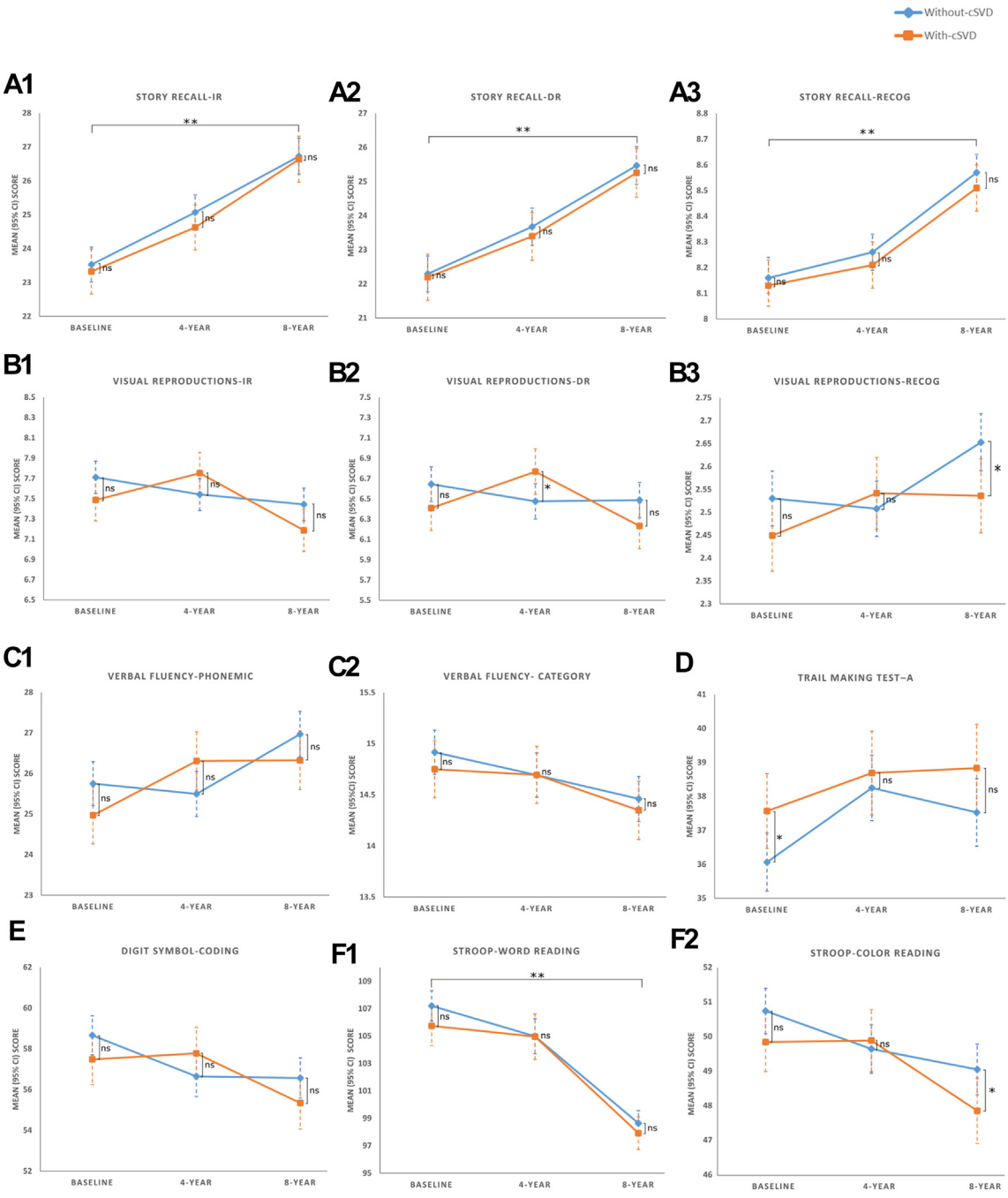

***Fig. 2:* Associations of cerebral small vessel disease (cSVD) and cognitive functions overtime.** Multivariable adjusted mean differences using linear mixed models for repeated measurements are plotted. In (2.A.1, 2.A.2 and 2.A.3), increase of logical memory functions (Story recall-immediate, delayed and recognition respectively) over time in both participants with **c**SVD and participants without **c**SVD groups; In (2.B.3), differential increase of visual reproductions-recognition score by **c**SVD groups; In (2.F.2), decline of Stroop-color reading in the participants with **c**SVD compared to the participants without **c**SVD group. Note: Significance levels are shown as *p < 0.05 and **p < 0.01; ns = Non-significant. Error bars represent 95% confidence intervals.

events) have been adopted in Korean context. Although, this practice-related gains are assumed to be highest at short intervals of retests, some of the previous studies have reported that learning effects may persist as long as 3–7 years or even longer.[44,45] The most likely reason for remembering the long lasting episodic memory with a

great details is probably the story with its context-sensitivity, as if in a personally experienced emotional event. On the other hand, some of the visual memory tests scores (e.g., visual reproductions-immediate and delayed) remained stable over time and did not differ significantly between the cSVD groups. A failure to attain practice-related gains can, however, be a predictive indicator of future cognitive decline.[46] In a previous study of amnestic mild cognitive impairment (aMCI) patients, those who showed minimal practice effects were at higher risk for cognitive decline after a year compared with patients who showed large practice effects.[47] Absence of practice effects even in cognitively normal (CN) individuals has been shown to predict Alzheimer's disease.[48] Although, our study was not designed to test learning effects, we found significant better performance in visual reproductions-recognition score in participants without cSVD, whereas, participants with cSVD remained stable over the time resulting in a significant difference at 8-year follow-up (with similar results observed for visual reproductions-immediate and delayed as well in the sensitivity analysis, Supplementary Table S2).

Our study has several limitations. First, we did not have data on some other radiological markers of cSVD (e.g., expanded perivascular space, brain atrophy and micro-infarcts). Although, some population based studies have reported weak or no association of expanded perivascular space (EPVS) and cognitive function,[49,50] brain atrophy was found to be associated with cognitive impairment.[51–53] However, our study subjects were pre-aging population (avg. age 58.5 years) and have shown low degrees of severity/counts on cSVD lesions that we read (Supplementary Table S5). The prevalence of lacune and microbleeds are quite low compared to the other population (both Western and Asian), which is probably why we did not observe steeper cognitive decline involving more cognitive domains. One of the possible underlying causes may be related to use of less sensitive MRI sequences in our study (conventional 2D T2*GRE sequences) compared to high-spatial-resolution 3D T2*GRE sequences that has shown to have a higher sensitivity in detecting cerebral microbleeds.[54] Second, we have had participants excluded from analysis because of incomplete data, missing covariates or lack of repeat neuropsychological testing (Fig. 1). However, our sample size was reasonably large and comparison of general characteristics have shown that excluded subjects were older, less educated and had more chronic conditions (e.g., hypertension and diabetes) than the included participants (Supplementary Table S4). Therefore, we believe that it may not have biased our results as we retained relatively younger and healthier subjects. Nonetheless, a potential selection bias cannot completely be ruled out. Third, since we tested several number of individual cognitive functions, it could have led us to an increased risk of Type I error due to multiple testing phenomenon. However, we chose to not adjust for multiple comparisons as they can also increase the type II error rate.[55] Fourth, there might be an underestimation of cognitive function decline overtime in our study due to healthy cohort effect. Participants were originally enrolled in 2001 and since then there might be high awareness of hypertension and concurrent treatment. Additionally, the unique health systems in South Korea where regular health check-ups (every 2-year) are available for general population may limit the generalizability of our study findings in a relatively resource-poor health set-ups.[56] Finally, we followed up middle-aged subjects to investigate the relationship between cSVD and cognitive functions, but not the link between cSVD and clinical diagnosis of dementia (e.g., cognitive function affecting activities of daily living). However, a study of this nature would be far more complex, any may need even longer follow-up period.

Conclusion

In conclusion, the presence of cSVD may be an important risk factor of cognitive decline, especially executive functioning, and thus, early prevention of cSVD would help preserving cognitive function in normal aging population. Future studies with more precise quantification of cSVD and longer follow-ups in the middle-aged population are warranted for further prediction of cognitive outcomes.

Contributors

A.T.S., Y.H.H., S.K., S.K.L., and C.S. conceptualized and designed the study. A.T.S. performed all statistical analyses. All authors participated in the interpretation of data, drafting of the manuscript and critical revision of the manuscript. S.K.L., S.K., C.S. gave data collection, administrative, technical, or material support. C.S. and A.T.S. had full access to all the data and verified the data in the study and were responsible for the decision to submit the manuscript.

Data sharing statement

Data are not publicly available and can only be used in the form of de-identified participant data by those included in the institutional review board plan. Data requests should be made online to the Korea National Institute of Health or via email (whalwls0227@korea.kr).

Declaration of interests

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101284.

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