Cognitive impairment in sporadic cerebral small vessel disease

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THEORETICAL ARTICLE

Cognitive impairment in sporadic cerebral small vessel disease: A systematic review and meta-analysis

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Abstract

This paper is a proposal for an update on the characterization of cognitive impairments associated with sporadic cerebral small vessel disease (SVD). We pose a series of questions about the nature of SVD-related cognitive impairments and provide answers based on a comprehensive review and meta-analysis of published data from 69 studies. Although SVD is thought primarily to affect executive function and processing speed, we hypothesize that SVD affects all major domains of cognitive ability. We also identify low levels of education as a potentially modifiable risk factor for SVD-related cognitive impairment. Therefore, we propose the use of comprehensive cognitive assessments and the measurement of educational level both in clinics and research settings, and suggest several recommendations for future research.

KEYWORDS
cerebral small vessel disease, cognitive ability, lacunar stroke, meta-analysis, systematic review, vascular cognitive impairment, vascular dementia

1 | CONTEXT FOR THE "HYPOTHESIS"

The term small vessel disease (SVD) refers to a collection of neuroimaging and neuropathological abnormalities found in the brain's white and deep gray matter. Visible radiological markers of the disease include white matter hyperintensities (WMH) and lacunes of presumed vascular origin, cerebral microbleeds, visible perivascular spaces, and cerebral microinfarcts. These markers likely reflect multiple pathological changes affecting the brain's small vessels, such as endothelial dysfunction, impaired cerebral blood flow, and reduced vessel pulsatility, although the relationships among these mechanisms are complex and not yet fully understood.[1,2] SVD is the primary cause of vascular cognitive impairment (VCI) in older age. The meaning of the term VCI has been refocused several times in recent years,[3-5] but broadly refers to cognitive impairments due to underlying vascular contributions, which can range in severity from subtle subclinical decline in cognitive ability, to mild cognitive impairment (MCI) and dementia.[7,8] In this review, we use the term "impairment" to denote any reduction in cognitive ability relative to an individual's typical ability, as opposed to a normative standard, or a diagnostic construct, unless otherwise stated.

1.1 | Why is SVD-related cognitive impairment important?

As life expectancies across the world continue to rise, so too does the predicted global burden of age-related cognitive impairment, including VCI. In all societies, the economic impact of cognitive impairment

is tremendous. Individuals with cognitive impairment use more healthcare services and require greater support with activities of daily living, either from unpaid family carers, or from paid care services.[9,10] In 2002, a review of the costs associated with VCI in Canada estimated the average annual cost per individual to be between CAD $15,022 (USD equivalent $9,313) for mild VCI, and CAD $34,515 (USD equivalent $21,399) for severe VCI.[10] Equally as striking is the personal impact upon individuals experiencing cognitive impairment, who are at greater risk of anxiety and depression and report having a lower quality of life.[11,12] A reduction in the incidence or progression of cognitive impairment, therefore, is a key target for clinical trials of treatments or interventions for SVD. Any intervention that improves cognitive outcomes in SVD has the potential to alleviate the burdens it places on individuals and on our societies, and would be a step toward reducing rates of VCI and multiple major dementias.

1.2 | What kind of cognitive impairments are associated with SVD?

To accurately assess cognitive ability in SVD and how it might change in response to intervention, researchers must use cognitive tests that are sensitive to the cognitive impairments caused by SVD. However, despite a huge number of studies on the subject, the nature of cognitive impairments in SVD remains poorly characterized. Current consensus statements suggest that the disease primarily affects the domains of processing speed and executive function, but that memory and language abilities remain relatively well preserved.[13,14] Processing speed refers to the speed at which a person can understand and respond to information.[15] Executive function is a broader concept encompassing skills such as planning, organization, and switching attention, which enable goal-directed behaviors.[15] This profile of SVD-related cognitive impairments is frequently reported in the research literature, but the studies underpinning this suggestion are conflicting and require careful consideration. First, many of the studies examining SVD-related cognitive impairments have small participant samples, so could be insufficiently powered to detect cognitive deficits. Second, many of these studies focus on narrowly defined subtypes of SVD (ie, genetic SVDs), or on those with a high disease burden who may not represent the full spectrum of sporadic SVDs. We also anticipate that some studies may be influenced by expectations of the cognitive impairments they will observe. Based on the understanding that SVD causes deficits in executive function and processing speed, studies might carry out tests that measure only those abilities and neglect to test for impairments in other abilities such as memory, which are more typically associated with dementia.

To gain an unbiased overview of the nature of cognitive impairments associated with SVD, we carried out a systematic review and meta-analysis of studies reporting cognitive data for cohorts with clinical or radiological evidence of SVD, and control cohorts without SVD (see Figure 1; full details of the Methods and Results are provided in Section 2). As expected, the sample sizes of the SVD cohorts were small, ranging between 4 and 196 participants (median: 27). Four studies conducted power calculations,[52,57,71,85] but only one of these studies included a sample size sufficient to detect differences in cognitive performance between groups, according to their own calculations.[57] We carried out seven separate meta-analyses to examine differences in performance between SVD and control groups in seven cognitive domains: executive function, delayed memory, processing speed, language, visuospatial ability, reasoning, and attention. The results of our meta-analyses suggested that individuals with SVD performed more poorly than controls on cognitive tests in each cognitive domain that we examined. Our findings concur with those of a recent meta-analysis of 27 studies by Vasquez and Zakzanis,[16] which compared the cognitive abilities of participants with vascular cognitive impairment without dementia and control subjects, finding deficits in a similarly broad range of domains. Contrary to current consensus, our results suggest that the cognitive impairments associated with SVD extend beyond executive function and processing speed, to affect all major domains of cognitive ability.

Typically, multiple cognitive abilities are recruited to carry out an individual cognitive task. For example, a list learning task is broadly considered to be a test of memory, but performance of the task will also require language abilities to comprehend the words on the list, processing speed to process the verbal information, and so on. Therefore, deficits in a number of cognitive domains could result in poor performance on this memory task. Many cognitive tasks appear to require speed of information processing for efficient performance, and tests of processing speed are among those most affected by aging. As a

RESEARCH IN CONTEXT

1. Systematic review: We conducted systematic searches of MEDLINE, Embase, and PsycINFO. Identified literature contradicts current consensus statements on small vessel disease (SVD)–related cognitive impairments, which describe impaired information processing speed and executive functions, alongside preserved memory and language skills. Also, little is known about whether cognitive impairments vary between clinical presentations of SVD.
2. Interpretation: SVD-related cognitive impairments are global, affecting all cognitive domains examined. Global impairments were present regardless of SVD presentation (eg, stroke, mild cognitive impairment/dementia, or non-clinical cohorts). Our findings also highlight low levels of education as a potentially modifiable risk factor for SVD-related cognitive impairments.
3. Future directions: Future studies should test a broad range of cognitive domains, account for educational experience, and include multiple presentations of SVD, to examine vascular contributions to cognitive impairments and dementia.

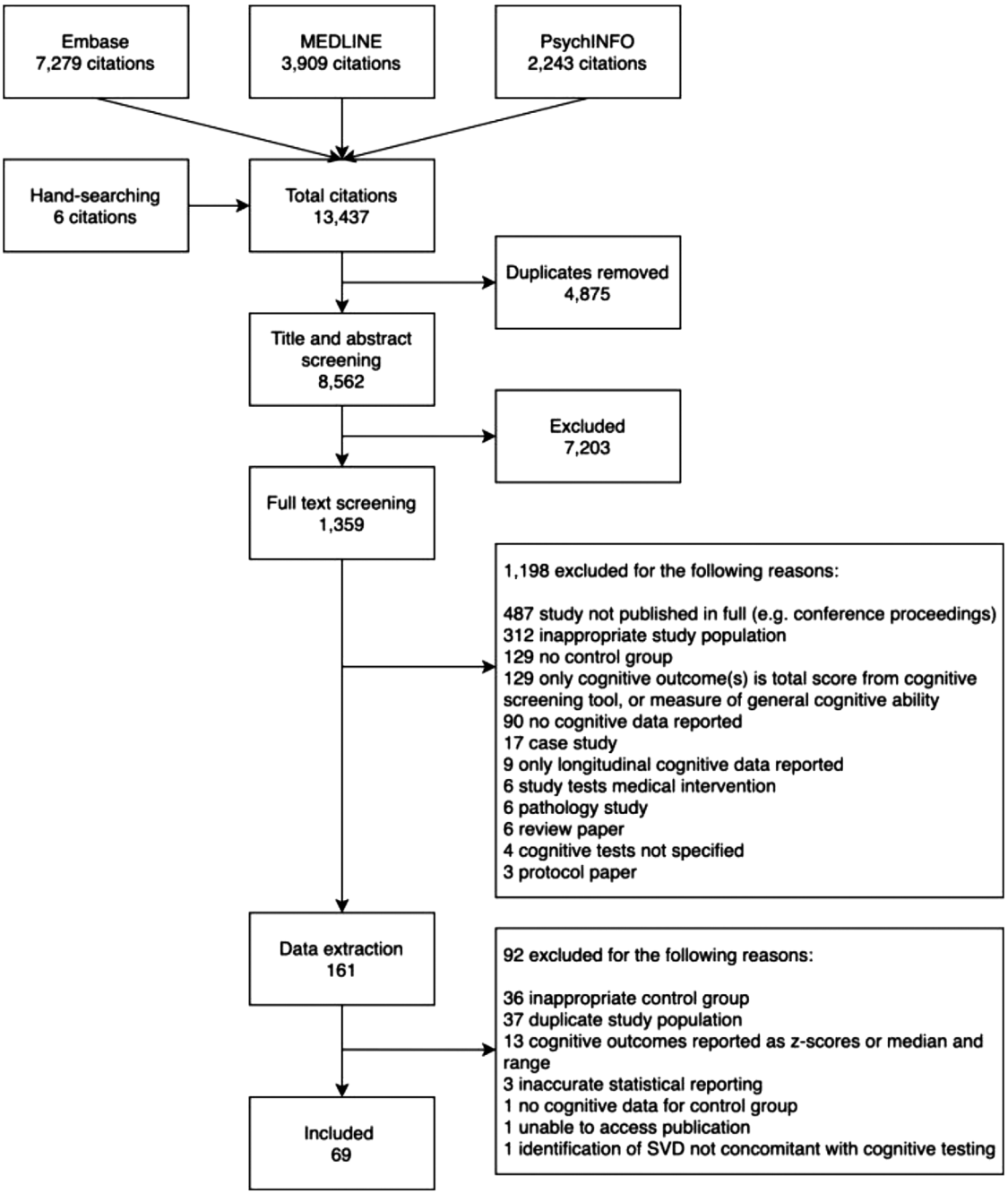

FIGURE 1 Flow diagram of systematic review screening process

result, it has been suggested that processing speed drives age-related changes in other fluid cognitive abilities.[17] Moreover, processing speed has been found to mediate, statistically, the association between brain white matter health and general cognitive ability in older people.[18] However, there is currently a more agnostic attitude to the place of processing speed; there is not considered to be definitive evidence about whether processing is the driver of age-related declines in other cognitive abilities, or whether it is just another domain of cognitive ability that declines on average with age.[19,20] Whereas the results of our meta-analyses suggest that relative to controls, cohorts with SVD have deficits in all major domains of cognitive ability, it remains to be examined whether these deficits could be the result of the early impairment of certain key domains of cognitive ability, or could be the result of impairment across multiple domains of cognitive ability more generally.

Growing evidence suggests that SVD-related cognitive impairments result from the disruption of white matter tract networks connecting regions of the brain that are critical for cognitive function.[21,22] Several cohort studies have suggested that the dysexecutive/slowed information processing profile typically associated with SVD could arise from strategic lesions that disrupt frontal-subcortical white matter projections, such as the anterior thalamic radiation and the forceps

minor.[23–26] However, visible infarcts represent only a proportion of the structural changes occurring in SVD. Microstructural alterations in WMH extend beyond the visible lesion, into the surrounding, normal-appearing peri-lesional tissue known as the "SVD penumbra".[27] Similarly, the impact of visible lesions can extend beyond local tissue, to affect distant brain regions.[28] Therefore, SVD-related structural brain changes are diffuse and likely affect white matter networks throughout the whole brain.[22,29] One analytic approach that has provided insight into the impact of SVD on the structural connectivity of the brain is the application of graph theoretic approaches to diffusion tensor imaging (DTI) tractography data. Whereas several studies adopting this approach have found reduced connectivity and efficiency of both local and global white matter networks, associations between these changes and impairments in specific cognitive domains remain unclear.[22]

1.3 | Do cognitive impairments vary according to the clinical presentation of SVD?

In the majority of cases, SVD manifests sub-clinically with few overt symptoms. However, SVD also contributes to, and in some cases is the primary cause of, a spectrum of disorders ranging from stroke, to MCI, and multiple major dementias. SVD causes ≈20% of all strokes, increases the risk of recurrent ischemic stroke, and associates with poorer functional outcomes post-stroke.[30,31] SVD also contributes to ≈40% of all dementias and increases the odds of developing incident dementia.[32,33] Whereas stroke and dementia are often considered separately, they convey mutual risk to one another. For example, stroke doubles the chance of developing dementia,[34] and poor cognitive performance increases the risk of stroke.[35] Additionally, increasing evidence supports the hypothesis that stroke and dementia share underlying mechanisms.[36,37] For example, dysfunction of the blood–brain barrier (BBB) has been identified as one of the earliest detectable mechanistic changes in the preclinical stages of dementia, occurring prior to the development and accumulation of typical Alzheimer's disease (AD) biomarkers such as amyloid beta (Aβ) and phosphorylated tau.[38] Arterial stiffness, another pathological hallmark of SVD, has also been associated with the deposition of Aβ and its accumulation over time.[39] Vascular pathologies are now considered to contribute substantially to the cognitive deficits observed in most major forms of dementia, including AD. In a recent study examining carriers of the E4 variant of apolipoprotein E (*APOE4*), the primary susceptibility gene for AD, BBB breakdown in the hippocampus and parahippocampal gyrus was associated with poorer cognitive ability independently of Aβ or tau accumulation.[40] Whereas these findings have yet to be replicated, they suggest that this gene variant might contribute to AD and its resultant cognitive decline through BBB dysfunction, rather than solely through more traditional AD biomarkers. In 2017 the World Health Organization highlighted the prevention of stroke via the management of traditional vascular risk factors (eg, smoking, high blood pressure, high cholesterol, diabetes) as a means of preventing dementia.[6] However, despite increasing recognition of cerebrovascular contributions to neurodegenerative disease processes,[41] little is known about how cognitive impairments might differ across different SVD presentations. Patients who experience stroke and dementia have differing routes into clinical care, are treated by different specialists, and are recruited into different research studies, often preventing direct comparison of their cognitive symptoms.

We categorized the SVD cohorts in our sample into three groups based on the clinical characterizations and recruitment settings detailed in the original publications. These three groups included: (1) non-clinical SVD cohorts (cohorts who exhibited radiological evidence of SVD, but had no specific clinical or cognitive symptomatology); (2) cohorts who presented with stroke; and (3) cohorts with subjective or objective cognitive impairments, or dementia (further detail on cohort categorization is provided in Section 2). To some extent, our three SVD presentation categories may represent a continuum; individuals with radiological evidence of SVD but no overt clinical symptoms may go on to experience stroke and/or dementia. Additionally, owing to the inter-related nature of stroke and dementia, it is possible that cohorts in these three categories exhibit both vascular and neurodegenerative pathologies. As expected, tests of processing speed, executive function, attention, and reasoning were most frequently carried out in cohorts with stroke and tests of delayed memory, visuospatial ability and language were most commonly carried out in cohorts with cognitive impairments (see File S1 in supporting information).

The results of meta-regression models investigating differences in cognitive performance of the three SVD presentation groups (relative to controls) indicated differences in the magnitude of cognitive effect sizes among the three groups, such that cohorts with cognitive impairment/dementia performed worse than non-clinical cohorts on tests of executive function, delayed memory, and visuospatial ability, and worse than stroke cohorts on tests of delayed memory only. It is possible that the inclusion of samples with cognitive impairments (including MCI and dementia) could be driving the findings that SVD cohorts overall performed more poorly on tests of memory than control cohorts. However, visual inspection of a forest plot for memory (Figure 2) suggests that this is unlikely to be the case as almost all cohorts in each presentation group show deficits relative to control cohorts.

1.4 | How do risk factors for SVD affect cognitive impairment?

Age is the primary risk factor for the development and progression of SVD. The prevalence of magnetic resonance imaging (MRI) markers of SVD increase with age and are found in the majority of individuals over the age of 60. In contrast, it is unclear whether biological sex may act as a risk factor for SVD,[42,43] although the under-recruitment of women in stroke research may limit knowledge,[44] and the lack of sex-disaggregated reporting limits the scope of meta-analyses on this topic. Owing to their potential for modification, traditional vascular risk factors (VRFs) such as hypertension, diabetes, and hypercholesterolemia have received a great deal of attention, alongside lifestyle factors such as smoking, lack of exercise, poor diet, and high salt intake.

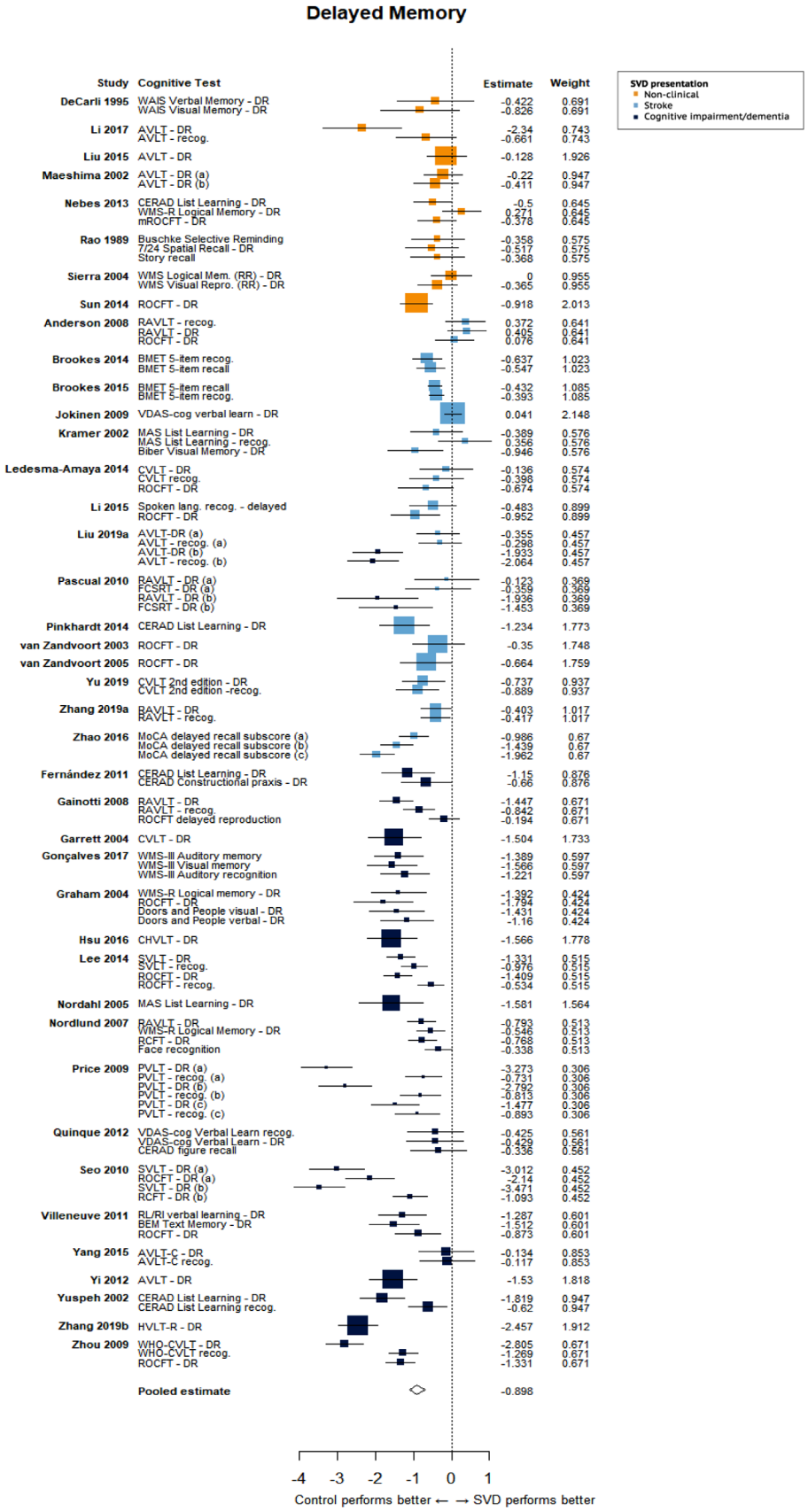

FIGURE 2 Forest plot of meta-analysis of tests of delayed memory. The effect size metric is a standardized mean difference. The sizes of the squares reflect the weight given to each effect size. Letters in brackets indicate different SVD cohorts in a given study

Each has been associated with increased SVD risk, but trials of risk-lowering interventions have produced mixed results.[1] Additionally, a recent meta-analysis of early life risk factors for SVD found lower childhood socioeconomic status, lower childhood IQ, and fewer years of education to be associated with increased radiological burden of SVD,[45] although these risk factors are related to one another and may convey interdependent effects.

Due to their associations with an increased brain burden of SVD, each of these risk factors has the potential to impact cognitive ability. Therefore, it is important that these factors are accounted for statistically (where appropriate) and considered carefully when interpreting study results. Of the studies included in our meta-analysis, almost all reported data on the age, sex, and education of study cohorts, however, reporting of vascular risk data was less complete (see File S2 in supporting information). Approximately half of all studies reported history of hypertension or diabetes, and only one third of studies reported smoking status, despite its known association with SVD progression. Vascular risk data were least often reported for cohorts with a cognitive presentation of SVD, which could suggest that these factors are percieved as being less relevant to cohorts with MCI or dementia.

We carried out further meta-regression analyses to investigate whether differences in age, education, or the prevalence of hypertension or diabetes between SVD and control cohorts accounted for the cognitive effects we observed in our meta-analyses. The results of these analyses suggest that differences in years of education between SVD and control groups account for a proportion of the differences in cognitive test scores in the domains of memory, executive function, and visuospatial ability. All other cognitive domains showed a similar direction of effect (albeit non-significant) except processing speed, which could support the suggestion that processing speed might be less amenable to beneficial effects of education than other cognitive abilities.[46] These findings highlight education as a (potentially modifiable) risk factor for SVD-related cognitive impairment, emphasizing the importance of accounting for education in analyses of cognitive change over time, or comparisons of cognitive ability between groups. An additional factor for consideration that is closely related to educational level is peak (or premorbid) cognitive ability. In any analysis of cognitive decline, observed levels of cognitive ability will be relative to an individual's prior abilities.[47] Despite this, peak cognitive ability is seldom considered in clinical studies. Of the 69 studies included in our meta-analysis, only seven[52,56,57,64,66,92] estimated peak ability and only two of these studies included this score as a covariate in their analyses.[56,92]

1.5 | Summary of findings and recommendations for future work

Based on 3229 individuals with SVD and 3679 control participants from 69 studies, our meta-analyses demonstrated that SVD-related cognitive impairments affect all major domains of cognitive ability. To accurately assess the full extent of SVD-related cognitive impairments, we recommend the use of comprehensive test batteries that cover a range of cognitive domains, such as that proposed by the National Institute for Neurological Disorders and Stroke (NINDS) and the Canadian Stroke Network (CSN[48]). This test protocol is designed for use with participants with VCI and assesses a broad range of cognitive abilities. The full-length protocol takes 60 minutes to administer, but can be shortened to 30 or 5 minutes, while still capturing information from a fairly broad range of cognitive abilities. Widespread use of a standard cognitive testing protocol will also facilitate more accurate cross-comparison or meta-analysis of cognitive data from different studies.

The majority of studies in our meta-analysis had small sample sizes, and very few studies carried out power calculations. To make inferences about cognitive impairments in SVD, it is of vital importance that studies are adequately powered to detect cognitive effects. This meta-analysis summarizes 69 publications on a broad range of SVD presentations—references 52 to 120 provide a useful database of effect sizes, which can be consulted and used to estimate power calculations in future studies.

The results of our first meta-regression analysis suggested that cohorts with a cognitive presentation of SVD performed more poorly than cohorts with non-clinical presentations of the disease on tests of delayed memory, executive function, and visuospatial ability, and more poorly than cohorts with stroke presentations on tests of delayed memory. Our grouping of cohorts into their respective SVD presentation categories was based on cohort descriptions, recruitment settings, and diagnostic criteria, all of which varied considerably between studies. A more effective approach to characterizing SVD subtypes would be to recruit subjects with differing presentations of SVD into the same study, which would facilitate comparison of cognitive and other clinical outcomes.

As we have described, vascular disease and neurodegeneration are interrelated. Where possible, data should be collected that is relevant to both vascular and neurodegenerative disease processes. In terms of cognitive data, this would mean collecting data from a broad range of cognitive domains, as previously recommended. In terms of neuroradiological data, this would mean considering radiological markers of SVD (WMH, enlarged perivascular spaces, lacunes, microbleeds, microinfarcts, altered diffusion tensor imaging metrics), and those more commonly associated with neurodegeneration such as cerebral atrophy and hippocampal volume. The collection of vascular risk data is also important. History of hypertension, diabetes, and smoking status are quick to ascertain and should be collected for all individuals with suspected SVD in clinical and research settings. The collection of vascular biomarkers at different stages throughout the development of dementia may also provide an indication of the changing contributions of vascular dysfunction to neurodegenerative disease processes over time. Through a more complete exploration of the risk factors, brain changes, and cognitive consequences that are shared between stroke and dementia, more accurate characterization of SVD subtypes and their precipitating factors might be possible.

Finally, the results of our second set of meta-regression analyses indicated that level of education is associated with the severity of SVD-related cognitive impairments. We strongly recommend that future studies account for educational level or peak cognitive ability when

examining cognitive change over time, or comparing cognitive ability between groups. A range of methods can be used to estimate peak cognitive ability, some of which are free and have been validated in multiple languages.[49]

2 | APPENDIX

2.1 | Methods

We performed this systematic review and meta-analysis in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The review protocol is registered on the PROSPERO database (ID: CRD42017080215).

2.1.1 | Search strategy and study selection criteria

We developed and tested a detailed search strategy (see File S3 in supporting information) to identify studies reporting the results of cognitive testing in a cohort with SVD (performed contemporaneous with identification of SVD), and a control cohort with no history of neurological or psychiatric conditions. We searched OVID MEDLINE, Embase, and PsycINFO, for human studies published in any language from January 1, 1985, when MRI became more widely available in clinical practice, to October 6, 2019. To identify additional studies, we checked the reference lists of relevant review articles and hand-searched the previous 7 years of *Stroke* and the *Journal of Cerebral Blood Flow and Metabolism*. Study inclusion and exclusion criteria are presented in File S4 in supporting information.

2.1.2 | Data extraction

Two authors (OH and EB) independently extracted key information, which included group-level demographic data for the SVD and control groups (age, sex, education), group-level data on vascular risk factors (% cohorts with hypertension, diabetes, hypercholesterolemia, and smoking status), group-level data on WMH burden, and group-level cognitive test scores for SVD and control groups. The vast majority of cognitive data were presented as mean and standard deviation. To avoid introducing additional heterogeneity into the meta-analysis dataset, we did not convert cognitive data presented as median and range to mean and standard deviation—instead these data are summarized in File S5 in supporting information. Where individual participant data were presented, we calculated the mean and standard deviation of the variables we extracted. Cognitive data were then categorized into seven domains of cognitive ability: information processing speed, executive function, delayed memory, attention, reasoning, visuospatial ability, and language. However, it is important to note that subdomains of cognitive ability are not discrete, and that individual cognitive tests often engage abilities from multiple cognitive domains. To ensure that tests were reliably categorized according to the cognitive domain that they are considered to primarily assess, two authors experienced in neuropsychological testing (OH and AJ) independently categorized cognitive data into the seven domains listed above and resolved disagreements by consensus (see File S6 in supporting information for further information). Studies reported a wide range of memory tests, including tests of long-term, short-term, and working memory. To reduce heterogeneity in the dataset, we included only tasks featuring a delayed recall/recognition component, as these were the most frequently reported memory tasks. We excluded data for which we could not identify the specific test score (eg, where authors reported results for a Trail Making task, but did not specify whether the score was for Trail Making A, Trail Making B, or Trail Making A-B). We also excluded data for which we could not discern whether a higher or lower score indicated better performance. Where studies reported multiple scores for one cognitive test (eg, for the Wisconsin Card Sorting Test: number of perseverative errors, total number of errors, number of categories, etc.), we included the score most commonly reported in the meta-analysis dataset. Due to the large number of included studies and the large number of variables used in our analyses (ie, sociodemographic, cognitive, and vascular risk variables), we did not contact the authors of original publications to obtain missing data.

2.1.3 | Statistical analysis

We calculated a standardized mean difference (SMD) to represent the difference between performance of the SVD and control cohorts on each cognitive test. We multiplied the SMD by −1 for tests on which a lower score indicated better performance. We excluded three studies due to reporting of implausibly large effect sizes, which upon examination appeared to be due to statistical or reporting errors in the original publications. While several larger effect sizes (SMD > 3) remain in our meta-analyses, these effect sizes come from small study samples so are unlikely to affect results if omitted.

2.1.4 | Meta-analysis models

We ran seven separate random effects meta-analyses to assess the differences in performance between SVD and control groups on cognitive tests in each cognitive domain. We conducted all meta-analyses using the robumeta package[50] in R version 3.6.1.[51] robumeta permits the meta-analysis of multiple effect sizes from one study using robust variance estimation (RVE) to account for their statistical dependency. This approach maximizes the amount of data included from a single study, increasing the statistical power of each meta-analysis. Dependency in our dataset arose from the inclusion of multiple effect sizes from the same study sample, and the inclusion of studies that used the same control group as a comparison for multiple SVD groups. Covariance matrices for multiple outcomes arising from a single study are rarely published; therefore, robumeta imputes a user-specified value

for the within-study effect size correlation. We were conservative in our choice of within-study effect size correlation—we specified rho as 0.8 and carried out sensitivity analyses in robumeta, which impute rho values at increments of 0.1 to test whether this alters the model results. For all analyses, we weighted effect sizes according to a correlated effects dependence structure within the robumeta package and used small sample size corrections. Small sample corrections, which correct both the residuals and degrees of freedom (df) used in the RVE, increase the accuracy of models including <40 studies.[50] After correction, if the Satterthwaite df for the model are less than four, the *P* value is considered unreliable due to the probability of type I error being greater than 0.05. In our analyses, results of models with Satterthwaite df < 4 were considered unreliable. We report I^2 and τ^2 as measures of heterogeneity.

2.1.5 | Meta-regression models

We carried out two secondary analyses to examine the following study-level and cohort-level variables:

1 SVD presentation

To test whether the pooled study effect size differed according to SVD presentation, we grouped each SVD cohort into one of three categories according to the characterization of the cohort and recruitment setting detailed in the original publication (see File S7 in supporting information).

a) Stroke presentations

Cohorts in this category most commonly presented to stroke or neurology services with symptoms of lacunar syndrome, with or without evidence of corresponding vascular lesions. Other cohorts in this category had radiologically identified SVD, or subcortical ischemic vascular disease.

b) Cognitive presentations

Cohorts in this category were identified on the basis of impaired cognitive ability ranging from MCI to vascular dementia. Typically, cohorts presented with cognitive impairment (according to clinical diagnosis, objective cognitive testing, or subjective concern) and either radiological evidence supporting a vascular etiology, or multiple risk factors for cerebrovascular disease.

c) Non-clinical presentations

Non-clinical cohorts had radiological evidence of SVD (WMH or lacunes of presumed vascular origin), but no clinical diagnosis. Typically, cohorts were community-dwelling older individuals recruited within a defined geographical region, or via community advertising. Several cohorts in this category presented to clinical services with non-specific symptoms such as dizziness or headache, but received no diagnosis upon examination.

We then entered SVD presentation as an ordinal predictor in the meta-regression model for each cognitive domain, with the cognitive presentation category as the reference group.

2 Differences in the prevalence of vascular risk between the SVD and control cohorts

All extracted cognitive data were unadjusted for demographic or vascular risk factors. Therefore, to test whether differences in age, education, hypertension, or diabetes between SVD and control cohorts accounted for study effect sizes, we calculated the difference in age, years of education, % sample with hypertension, and % sample with diabetes (eg, difference in age = mean age of control cohort – mean age of SVD cohort), and entered these variables as predictors in separate univariate meta-regression models for each cognitive domain.

2.1.6 | Quality assessment

Quality assessment criteria (see File S8 in supporting information) were devised according to STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines. Two authors (OH and EJ) independently assessed the quality of included publications on a scale ranging from 0 to 8 and resolved disagreements by consensus. To assess whether the inclusion of lower quality studies affected the results of the meta-analyses, we re-ran meta-analysis models excluding studies with quality scores lower than the median quality score of the meta-analysis sample.

2.2 | Results

We identified 69 studies for inclusion in the review[52-120] (see Table 1)), which reported data for 89 cohorts with SVD (n = 3229), and 71 control cohorts (n = 3679; demographic data for the SVD and control cohorts are presented in Table 2). We did not pre-select literature that focused on a certain lesion type, or clinical, cognitive, or behavioral presentation of SVD, therefore, our dataset included SVD cohorts recruited from specialized cerebrovascular clinics; memory clinics; hospital-based stroke, dementia, and general neurology services; non-specialist medical centers; a stroke research network; and also included several research cohorts of healthy community-dwelling individuals. Included studies were from 18 countries in six continents, published in four languages.

2.2.1 | Meta-analyses

The pooled estimated effect size for each meta-analysis demonstrated that on average, control cohorts outperformed SVD cohorts on cognitive tasks in every domain examined (see Table 3 and forest plots in

TABLE 1 Characteristics of all included studies

Study	SVD cohort described as	SVD n	Control n	SVD age mean (SD)	SVD % female	SVD years of Education mean (SD)	SVD % Hyperte-nsion	SVD % Diabetes	SVD % Ever smoking	Variables on which SVD & Controls are matched (blank cells = no matching, or data unavailable)	SVD Mean WMH/TIV (SD) *Mean Visual rating (SD)*
Anderson[52]	Lacunar syndrome	30	30	68.3 (16.8)	47%	9.7 (2.12)				1, 2	
Atwi, 2018[53]	Fazekas ≥ 2	18	28	72[5]	56%		22%	6%		1, 2, 3	9.2 ml (0.6)
Bella, 2016[54]	VCI-ND	25	20	67.5 (6.7)	60%	7.6 (3.9)	88%		28%	1, 3	
Boone, 1992[55]	1. WMH ≤ 1 cm^2 2. WMH > 1 cm^2 - 10 cm^2 3. Total WMH > 10 cm^2	27 21 6	46[a]	63.6 (9.9) 69.2 (6.8) 72.0 (4.9)		15.0 (1.9) 14.2 (3.1) 12.8 (1.3)				3 3 3	
Brookes, 2014[56]	SVD	45	80	69.7 (8.2)	44%	Highest formal qualification: None: 51% Secondary: 11% Further education.: 27% Degree: 9% Higher degree: 0% Unavailable: 2%	84%	21%	69%	1, 2	Modified Fazekas n (%): Fazekas 0: 6 (13%) Fazekas 1: 12 (27%) Fazekas 2: 12 (27%) Fazekas 3: 12[27] Unavailable: 3 (6%)
Brookes, 2015[57]	SVD	196	303	63.5 (9.9)	32%	13.7 (3.8)	75%	23%	44%	1, 2, 4	
DeCarli, 1995[58]	WMH volume > 0.5% TIV	5	17	74[14]			0%			1	WMH/TIV 0.80 (0.24)
Deguchi, 2013[59]	Lacunar infarction	76	105	73.4 (8.9)	34%	12.5 (2.3)	68%	30%	13%[a]	1, 2	
Fang, 2013[60]	1. Silent brain infarct 2. Microbleeds 3. Silent brain infarct + microbleeds	46 41 49	91[a]	70.9 (6.4) 70.6 (5.2) 72.1 (5.0)	57% 42% 47%	8.11 (2.3) 8.24 (1.9) 8.20 (2.3)	83% 81% 82%	22% 27% 25%	20% 22% 25%	1, 2, 5 1, 2, 5 1, 2, 5	
Fernández, 2011[61]	MCI with subcortical vascular damage	19	19	72.2 (7.6)	32%	3.6 (3.5)					
Gainotti, 2008[62]	MCI + multiple subcortical infarcts	41	65	71.7 (5.9)	41%	Reporting unclear				1, 3	

(Continues)

TABLE 1 (Continued)

Study	SVD cohort described as	SVD n	Control n	SVD age mean (SD)	SVD % female	SVD years of Education mean (SD)	SVD % Hyperte-nsion	SVD % Diabetes	SVD % Ever smoking	Variables on which SVD & Controls are matched (blank cells = no matching, or data unavailable)	SVD Mean WMH/TIV (SD) *Mean Visual rating (SD)*
Garrett, 2004[63]	VCI-ND	18	25	78.4 (6.4)	44%	13.6 (2.5)					
Gonçalves 2017[64]	Subcortical vascular dementia	16	40	74.94 (5.4)	38%	3.2 (1.8)				1,2	
Graham, 2004[65]	VaD	19	19	71.2 (7.8)	26%	11.6 (3.1)				1, 3	
Hassan, 2010[66]	Symptomatic lacunar infarction	30	12	59.1(9.5)	40%	Able to read and write: 53% Educated to between primary and university level: 46.7%	100%	47%	53%	1	
Hsu, 2016[67]	MCI due to SIVD	20	30	68.5 (10.8)	30%	7.6 (4.17)	40%	25%		1,2,3	*23.9 (9.9) Scheltens*
Ishii, 2007[68]	1. CDR 0, non-strategic CVD 2. CDR 0, strategic CVD 3. CDR 0.5, non-strategic CVD 4. CDR 0.5, strategic CVD	68 38 21 21	234[a]	74.9 (7.9) 73.0 (6.3) 79.1 (6.9) 80.7 (6.5)		8.3 (1.5) 8.4 (2.1) 7.3 (2.2) 7.6 (1.7)	84% 92% 76% 86%	10% 16% 14% 5%			
Jokinen, 2009[69]	SIVD	89	524	73.6 (4.9)	48%	8.8 (4.2)	80%	18%	15%[a]	1, 2	*WMH severity ratings: Mild: 0 Moderate: 10 Severe: 79*
Kim, 2018[70]	Subcortical VCI	61	19	78.7 (6.3)	72%	7.3 (5.1)				1,2,3	
Kramer, 2002[71]	SIVD	12	27	73.7 (6.2)		15.3 (2.6)				1, 3	
Kuriyama, 2018[72]	1. dWMH Fazekas grade 1 2. dWMH Fazekas grade 2 3. dWMH Fazekas grade 3	134 62 16	68[a]	69.3 (5.7) 71.5 (6.3) 73.8 (6.6)	31% 36% 38%	Reporting unclear	47% 57% 81%	12% 15% 6%	16%[b] 7%[b] 13%[b]	2	*PWMH ≥ grade 2 (de Groot classification), n (%):* *4 (3%)* *17 (27%)* *11 (69%)*

(Continues)

TABLE 1 (Continued)

Study	SVD cohort described as	SVD n	Control n	SVD age mean (SD)	SVD % female	SVD years of Education mean (SD)	SVD % Hypertension	SVD % Diabetes	SVD % Ever smoking	Variables on which SVD & Controls are matched (blank cells = no matching, or data unavailable)	SVD Mean WMH/TIV (SD) *Mean Visual rating (SD)*
Ledesma-Amaya, 2014[73]	Lacunar infarction	16	16	63 (9.4)	38%	7.1[4]	13%	8%		1,3	
Lee, 2014[74]	Subcortical vascular mild cognitive impairment	67	75	73.7 (6.7)	61%	9.0 (5.2)	75%	25%		2	34.9 mL (17.8)
Lewine, 1993[75]	1. Men with WMH 2. Women with WMH	4 6	4 6	35.2 (11.8) 43.3 (8.4)	0% 100%					1 1	
Li, 2001[76]	Leukoaraiosis	29	25	64.9 (6.8)		7.5 (6.8)				1, 2, 3	
Li, 2012[77]	Lacunar stroke with ischaemic leukoaraiosis	20	20	65.8 (8.4)	45%	Reporting unclear	60%		60%		
Li, 2015[78]	Symptomatic lacunar infarction	19	23	66 (12.0)	37%	8.5[3]	68%	37%	11%[a]	3	
Li, 2017[79]	Leukoaraiosis	13	13	63[6]	39%	10.3 (3.3)	69%			1, 2, 6	
Liu, 2008[80]	Subcortical small vessel infarction	60	52	73[8]	47%		27%	14%		1, 2, 3	
Liu, 2015[81]	WMH	30	30	78.2 (5.7)		8.4[2]	23%	11%		1, 3	
Liu 2019a[82]	1. Subcortical ischaemic vascular impairment impairment (pre-SVCI) 2. Subcortical ischaemic vascular disease with cognitive	25 29	27 [a]	70.5 (3.5) 70.5 (5.8)	36% 45%	10.6 (2.6) 9.4 (1.7)	56% 59%	40% 37%	20% 24%	1, 2, 3 1, 2, 3	12.6 ml (5.0) 19.8 ml (8.8)
Liu 2019b[83]	1. SVD without cognitive impairment 2. SVD with cognitive impairment	21 20	25 [a]	64.6 (10.9) 66.5 (7.9)	52% 50%	10.5 (3.6) 13.1 (3.8)				1, 2, 3 1, 2, 3	3.2 ml (3.0) 3.4 ml (4.1)

(Continues)

TABLE 1 (Continued)

Study	SVD cohort described as	SVD n	Control n	SVD age mean (SD)	SVD % female	SVD years of Education mean (SD)	SVD % Hyperte-nsion	SVD % Diabetes	SVD % Ever smoking	Variables on which SVD & Controls are matched (blank cells = no matching, or data unavailable)	SVD Mean WMH/TIV (SD) *Mean Visual rating (SD)*
Maeshima, 2002[84]	1. Silent brain infarct 2. pWMH	21 14	63 70	49.4 (5.6) 51.4 (6.6)	62% 57%	12.5 (2.1) 12.4 (2.1)	24% 21%	14% 29%		1, 2, 3 1, 2, 3	
Nebes, 2013[85]	WMH	26	40	75.1 (5.8)	65%	14.5 (2.7)				1, 2, 3	
Nordahl 2005[86]	MCI + severe WMH	11	20	77.6 (3.6)	55%	13.5 (1.5)	82%	27%		1, 3	WMH/TIV 3.9 (1.3)
Nordlund, 2007[87]	Vascular MCI	60	60	67.0 (7.3)	63%	11.2 (3.2)				1, 2, 3	
Oguro, 2000[88]	PWMH	18	9	73.6 (4.2)	61%	9.3 (3.2)			Scale unclear	1, 2, 3	
Pascual, 2010[89]	1. Vascular white matter disease without dementia 2. Vascular white matter disease with dementia	12 12	12 (cog-nitive data for 10 only)[a]	80.7 (5.2) 79.5 (4.6)	50% 50%					1, 2, 3 1, 2, 3	
Pinkhardt, 2014[90]	Small vessel cerebrovascular disease	25	19	75[58–91]	68%						*Fazekas pWMH 2.36; Fazekas dWMH 2.2 SD not reported*
Price, 2009[91]	Dementia with: mild leukoaraiosis moderate leukoaraiosis severe leukoaraiosis	73 44 27	24 [a]	78.5 (5.7) 81.0 (5.0) 79.4 (4.4)	82% 66% 81%	12.6 (2.8) 12.2 (2.8) 11.9 (2.1)				2, 3	*Junque score* *4.0 (2.8)* *12.0 (2.3)* *22.3 (4.4)*
Quinque, 2012[92]	Early cerebral microangiopathy	11	21	61.4 (6.3)	40%	13.8 (3.0)				1, 2, 3, 4	*8.3 (4.0) ARWMC*
Rao, 1989[93]	Leukoaraiosis	10	40	47.1 (7.8)	90%	14 (1.9)				1, 2, 3	
Schmidt, 1993[94]	WMH	74	76	61.3 (6.6)		11.4 (2.6)	4%			3	

(Continues)

TABLE 1 (Continued)

Study	SVD cohort described as	SVD n	Control n	SVD age mean (SD)	SVD % female	SVD years of Education mean (SD)	SVD % Hypertension	SVD % Diabetes	SVD % Ever smoking	Variables on which SVD & Controls are matched (blank cells = no matching, or data unavailable)	SVD Mean WMH/TIV (SD) *Mean Visual rating (SD)*
Seo, 2010[95]	1. Subcortical vascular MCI 2. Subcortical VaD	34 (cognitive data for between 30-34 only) 20 (cognitive data for between 15-18 only)	96 (cognitive data for 63 only)[a]	70.6 (6.4) 74.2 (6.1)	44% 55%	10.1 (4.8) 7.2 (5.5)	84% 100%	29% 30%		2, 3	
Sierra, 2004[96]	Hypertensive with WMH	23	37	55.2 (4.2)	39%	11.2 (3.7)	100%		22%	1, 2, 3	
Squarzoni, 2017[97]	Silent brain infarct	57	187	72.1 (3.4)	56%		68%	33%		1	
Sudo, 2013[98]	Vascular MCI	15	11	74.1 (8.1)	60%	8.9 (4.0)				1, 2, 3	*Fazekas rating, n (%)* *Fazekas 0: 0 (0%)* *Fazekas 1: 0 (0%)* *Fazekas 2: 7(47%)* *Fazekas 3: 8 (53%)*
Sun, 2014[99]	Mild WMH	51	49	65.3 (7.2)	55%	10.3 (3.4)	16%	10%	8%	1, 2, 3	
Tupler, 1992[100]	dWMH	48	18	69.9 (10.1)	69%	13.9 (4.2)					
van Swieten, 1991[101]	Hypertensive with confluent WMH	10	18	67.8 (5.3)	32%		100%	50%		1, 2	*Normal white matter = 20; focal lesions = 12; confluent lesions = 10*

(Continues)

TABLE 1 (Continued)

Study	SVD cohort described as	SVD n	Control n	SVD age mean (SD)	SVD % female	SVD years of Education mean (SD)	SVD % Hyperte-nsion	SVD % Diabetes	SVD % Ever smoking	Variables on which SVD & Controls are matched (blank cells = no matching, or data unavailable)	SVD Mean WMH/TIV (SD) *Mean Visual rating (SD)*
van Zandvoort, 2003[102]	Lacunar infarct in brainstem	17	17	60.1 (11.6)	29%	<6 years primary school: 0% 6 years of education (YoE): 6% 8 YoE: 0% 9 YoE: 47% 10-11 YoE: 23.5% 12-18 YoE: 23.5% > 18 YoE: 0%				1, 2, 3	
van Zandvoort, 2005[103]	Supratentorial lacunar infarct	26	14	60.5 (12.3)	38%	Scale unclear				1, 3	
Villeneuve, 2011[104]	MCI with confluent WMH	21	27	73.4 (5.1)	48%	12.4 (5.2)				1, 2, 3	*10.0 (3.1) Wahlund*
Wolfe, 1990[105]	Multiple lacunar infarcts	11	11	64.6 (6.0)	No information	10.1 (3.1)				1, 3	
Wong, 2007[106]	Stroke associated with SVD	32	42	72.8 (10.0)	44%	Scale unclear				1, 2, 3	56.9 ml (8.7)
Yamauchi, 2000[107]	Lacunar infarct	28	34	69.3 (6.3)	32%	8.9 (1.3)	21%	11%		1, 3	*Anterior WMH 3.6 (3.1) Posterior 3.6 (2.8) Scale – see publication*
Yang, 2015[108]	Vascular MCI	15	15	61.7 (6.2)	73%	9.3 (2.4)				1, 2, 3	
Yang, 2016[109]	Lacunar infarct	60	30	67.0 (7.0)	42%	7.2 (2.3)	58%	18%	38%[a]	1, 2, 3	
Yi, 2012[110]	Subcortical vascular MCI	26	28	66.7 (9.5)	58%	9.9 (4.4)				1, 2, 3	

(Continues)

TABLE 1 (Continued)

Study	SVD cohort described as	SVD n	Control n	SVD age mean (SD)	SVD % female	SVD years of Education mean (SD)	SVD % Hypertension	SVD % Diabetes	SVD % Ever smoking	Variables on which SVD & Controls are matched (blank cells = no matching, or data unavailable)	SVD Mean WMH/TIV (SD) *Mean Visual rating (SD)*
Yu, 2019[111]	Extensive SIVD	29	25	71.8 (11.0)	52%	14.4 (3.2)	75%	10%	58%	1, 2, 3	DWMH 2.55 (2.5) cm^3 PWMH 29.0 (21.6) cm^3
Yuan, 2012[112]	Leukoaraiosis	46	38	72.0 (6.0)	70%	8[4]	74%	61%		1, 2, 3	
Yuan, 2017[113]	Leukoaraiosis	50	50	71.7 (5.5)	58%	7.5 (4.3)	67%	50%	26%	1, 2, 3	
Yuspeh, 2002[114]	SVaD	29	38	74.1 (8.2)	35%	13.2 (4.4)				1, 2, 3	
Zhang 2019a[115]	SVD	77	39	70[11]	40%	Educational level: Low = 45% Medium = 35% High = 20%	64%	16%	25%	1, 2	WMH/TIV 0.014 (0.002)
Zhang, 2019b[116]	Amnestic MCI with Fazekas > 1	30	90	68.33 (5.3)	47%	12.30 (2.6)				1, 2	
Zhao, 2016[117]	1. Lacunar infarct 2. WMH 3. Lacunar infarct + WMH	62 60 61	55[a]	73.2 (4.7) 71.9 (4.2) 73.9 (3.8)	42% 38% 33%	10.7 (3.2) 10.9 (3.6) 10.5 (3.2)	76% 75% 78%	37% 33% 43%	31%[a] 23%[a] 34%[a]		
Zhou, 2009[118]	MCI due to SVD	56	80	67.3 (6.2)	36%	9.6 (3.1)				2, 3	
Zhou, 2014[119]	1. Subcortical vascular MCI 2. Subcortical vascular disease	79 82	77[a]	72.2 (7.1) 74.1 (7.1)	53% 51%	9.9 (3.3) 7.4 (3.3)	63% 73%	29% 22%	32%[b] 42%[b]	2	
Zi, 2014[120]	pWMH	16	16	62.0 (4.9)	56%	8 (6.3-10.3)	63%	19%	19%[a]	1, 2, 3	

Notes: Data are presented as mean (standard deviation) or median (range), unless otherwise stated. Controls matched for: 1 Age; 2 Sex; 3 Education; 4 Premorbid IQ; 5 Vascular risk factors; 6 history of hypertension. Where cells are blank, no data were available.

Abbreviations: CDR, Clinical Dementia Rating scale; CVD, cerebrovascular disease; dWMH, deep white matter hyperintensities; MCI, mild cognitive impairment; pWMH, periventricular white matter hyperintensities; SIVD, subcortical ischemic vascular disease; SVaD, subcortical ischemic vascular dementia; SVD, cerebral small vessel disease; TIV, total intracranial volume; VaD, vascular dementia; VCI, vascular cognitive impairment; VCI-ND, vascular cognitive impairment–no dementia; WMH, white matter hyperintensities.

[a]Same control group used as comparison for both/all SVD groups.

[b]Current smoker.

TABLE 2 Summary of sociodemographic and vascular risk data for SVD and control cohorts

	SVD cohorts		Control cohorts	
	Cohorts (n = 89)	Mean (SD or 95% CI)	Cohorts (n = 71)	Mean (SD or 95% CI)
Mean age[a]	88	69.3 (67.8, 70.9)	70	66.4 (64.6, 68.2)
% female	76	49.0 (15.9)	63	50.9 (15.0)
Mean years education[a]	67	10.3 (9.7, 10.9)	53	10.8 (10.1, 11.6)
% hypertension	48	66.7 (23.0)	34	37.8 (20.7)
% diabetes	45	25.5 (13.7)	31	17.1 (13.5)
% hypercholesterolemia	5	55.1 (20.0)	4	35.1 (12.3)
% history of smoking	28	28.3 (16.1)	16	25.6 (16.9)

[a]Mean age and mean years of education were calculated using random effects meta-analysis in the meta package in R version 3.6.1.[121] Only studies that presented group-level data for age and years of education as mean and standard deviation were included in these meta-analyses. We did not test for differences in age, sex, level of education, or vascular risk factors between the SVD and control groups as some studies only reported these data for the SVD group, therefore, comparisons would not include all participants contributing cognitive data to the meta-analyses.
Abbreviations: CI, confidence interval; SD, standard deviation; SVD, cerebral small vessel disease.

TABLE 3 Results of meta-analysis models for each cognitive domain

							Heterogeneity	
	Studies	Outcomes	Estimate (SE)	95% CI	Degrees of freedom	Uncorrected p value	τ^2	I^2
Processing speed	37	88	−0.885 (0.14)	−1.17, −0.60	35.8	2.3×10^{-7}	0.6	91.4
Executive function	58	188	−0.936 (0.08)	−1.09, −0.78	56.1	$<2 \times 10^{-16}$	0.4	87.6
Delayed memory	41	98	−0.898 (0.10)	−1.10, −0.69	39.6	7.2×10^{-11}	0.5	88.0
Attention	12	19	−0.622 (0.14)	−0.94, −0.31	10.6	0.001	0.2	80.8
Reasoning	16	25	−0.634 (0.14)	−0.93, −0.34	14.6	4.2×10^{-4}	0.2	76.5
Visuospatial ability	27	50	−0.720 (0.11)	−0.96, −0.48	25.3	1.3×10^{-6}	0.3	77.6
Language	24	42	−0.808 (0.10)	−1.01, −0.60	22.7	3.2×10^{-8}	0.3	81.2

Abbreviations: CI, confidence interval; SE, standard error.

Figure 2 and Figures S1–S6 in supporting information). I^2 values, which are an indicator of inconsistency between effect sizes in the meta-analyses, were high in each model.

2.2.2 | Meta-regression analyses

Our meta-analysis dataset included 26 cohorts with stroke presentations of SVD, 31 cohorts with cognitive impairment or dementia, and 32 cohorts with non-clinical presentations of SVD. There were no differences in years of education, or prevalence of hypertension or diabetes among the three SVD presentation categories, but cohorts with cognitive impairment/dementia were significantly older than those with non-clinical presentations of the disease ($P = .002$; see Table 4).

Meta-regression models investigating differences in cognitive effect sizes of the three SVD presentation groups indicated that the effect size for delayed memory was 0.83 standard deviations greater for the stroke cohorts (95% confidence interval [CI]: 0.44, 1.21; $P < .001$) and 0.85 standard deviations greater for non-clinical cohorts (95% CI: 0.40, 1.29; $P = .001$), than cohorts with cognitive impairment/dementia. We also found that the effect size was 0.49 standard deviations greater in the domain of executive function (95% CI: 0.10, 0.88; $P = .015$), and 0.68 standard deviations greater in the domain of visuospatial ability (95% CI: 0.30, 1.01; $P = .002$) for the non-clinical cohorts than the cohorts with cognitive impairment/dementia (see File S9 in supporting information for full results). Including SVD presentation as a predictor in meta-regression models had little effect on study heterogeneity.

Meta-regression models investigating the impact of differences in age, education, and the prevalence of vascular risk factors between SVD versus control groups on cognitive effect sizes, indicated that the difference in cognitive performance between SVD and control groups could be due to lower levels of education in SVD cohorts (see File S10 in supporting information for full results). For every 1 year of difference in education between SVD and control groups, the cognitive effect size decreased (indicating superior performance of the control groups) by an estimated 0.23 standard deviations in the domain of executive function (95% CI: −0.37, −0.09; $P = .004$), 0.28 standard deviations in the

TABLE 4 Demographics of SVD cohorts with non-clinical presentations of SVD, stroke, or cognitive impairment/dementia

	Non-clinical		Stroke		Cognitive impairment/dementia		
	% cohorts (n = 32)	Mean (SD or 95% CI)	% cohorts (n = 26)	Mean (SD or 95% CI)	% cohorts (n = 31)	Mean (SD or 95% CI)	Uncorrected *P* value[c]
Mean age[a]	100%	66.1 (62.8, 69.4)	96.2%	69.0 (67.0, 71.1)	100%	72.8 (70.9, 74.7)	.002[b]
% female	71.9%	53.2 (20.8)	92.3%	42.0 (8.5)	93.5%	51.6 (14.6)	.027
Mean years education[a]	68.8%	10.6 (9.5, 11.7)	61.5%	10.6 (9.4, 11.8)	93.5%	9.9 (8.8, 10.9)	.515
% hypertension	62.5%	60.3 (28.7)	65.4%	68.6 (17.6)	35.5%	75.1 (16.4)	.214
% diabetes	59.4%	23.4 (16.4)	61.5%	28.6 (12.7)	32.3%	24.4 (9.1)	.524

[a]Mean age and mean years of education were calculated using random effects meta-analysis in the meta: An R package for meta-analysis. R News 2007, 7(3), 40–45.[121] Only studies that presented group-level data for age and years of education as mean and standard deviation were included in these meta-analyses.
[b]Significant difference at $P < .01$ between non-clinical and cognitive impairment/dementia groups.
[c]P value refers to comparisons made by one-way analysis of variance.
Abbreviations: CI, confidence interval; SD, standard deviation; SVD, cerebral small vessel disease.

domain of visuospatial ability (95% CI: −0.46, −0.10; $P = .009$), and 0.31 standard deviations in the domain of language (95% CI: −0.46, −0.16; $P = .001$). Including education as a predictor in meta-regression models reduced I^2 values by ≈13% in the domain of visuospatial ability and language, suggesting that education may account for some of the variability in cognitive effect sizes in these domains. Overall, however, I^2 values remained high. This could be due to our use of group-level demographic and vascular risk data, which may limit power to detect interactions between individual-level covariates and cognitive effect sizes. Meta-analytic approaches using individual patient data are increasingly popular but rely upon the availability of patient-level datasets, which in our sample were rare.

The majority of the meta-regression models assessing the influence of age on cognitive effect size produced df < 4, suggesting that model results were unreliable. Therefore, we further investigated the potential influence of age by re-running meta-analysis models excluding studies in which SVD and control groups were not matched for age. In these analyses magnitudes of estimated effect sizes were similar to the initial meta-analysis models and all models remained significant. Meta-regression models investigating the impact of hypertension and diabetes on cognitive effects also produced df < 4 suggesting that model results were unreliable, likely due to the limited availability of vascular risk data.

2.2.3 | Study quality

The mean study quality score was 4.97 (median 5, range 2–8). The magnitudes of estimated effect sizes were comparable to those using the full meta-analysis dataset, and all models remained significant (see File S11 in supporting information). I^2 values reduced by a small amount in the domains of executive function, visuospatial ability, attention, and language, but increased in the other domains.

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AUTHOR CONTRIBUTIONS

The study was designed by OH and supervised by JMW and IJD. OH conducted the literature search and OH, EB, TR, AS, and CM screened papers for inclusion in the review. OH, EB, XL, and EJ extracted data from eligible papers. OH and AJ categorized cognitive test data into domains. OH analyzed and interpreted the data with contributions from JMW and IJD. OH wrote the first draft of the manuscript; all authors contributed to later versions.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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