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FEATURED ARTICLE

The clinical profile of cerebral small vessel disease: Toward an evidence-based identification of cognitive markers

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Abstract

There is no consensus on which test is more suited to outline the cognitive deficits of cerebral small vessel disease (cSVD) patients. We explored the ability of eight cognitive tests, selected in a previous systematic review as the most commonly used in this population, to differentiate among cSVD patients, controls, and other dementing conditions performing a meta-analysis of 86 studies. We found that cSVD patients performed worse than healthy controls in all tests while data on the comparison to neurodegenerative diseases were limited. We outlined a lack of data on these tests' accuracy on the diagnosis. Cognitive tests measuring processing speed were those mostly associated with neuroimaging cSVD markers. There is currently incomplete evidence that a single test could differentiate cSVD patients with cognitive decline from other dementing diseases. We make preliminary proposals on possible strategies to gain information about the clinical definition of cSVD that currently remains a neuroimaging-based one.

KEYWORDS
cerebral small vessel disease, cerebrovascular disease, clinical profile, cognitive impairment, cognitive tests, dementia, differential diagnosis, meta-analysis, neuropsychological assessment

1 | NARRATIVE

Cerebral small vessel disease (cSVD) defines a group of diseases that affect small arteries, arterioles, venules, and capillaries of the brain and encompasses several pathological processes and etiologies.[1] The sporadic age-related cSVD type is the most frequent, but genetic forms such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) also exist.[2] Stroke, cognitive decline, and disability are major consequences of cSVD.[3] At present, the lack of specific preventive and therapeutic approaches does not allow reduction of the burden of these clinical sequelae.

As in other dementing conditions, the range of cognitive deficit severity in cSVD comprises a spectrum extending from mild cognitive impairment (MCI) to dementia.[4] Some cSVD patients may even be totally asymptomatic from the cognitive point of view. In patients with cSVD, the pattern of cognitive deficits seems to involve information processing; ability to focus, maintain, or shift attention; and ability to manipulate, organize, and select information.[5] Despite the common belief that the cognitive profile of cSVD is mainly characterized by attentional and executive dysfunctions, evidence for this is still scarce, and therefore efforts are needed to clarify the potential of available neuropsychological tests in identifying cSVD patients.

1.1 | In search of a cognitive marker for cerebral small vessel diseases

Over the past several years, there has been a great effort to define cSVD in vivo and this has resulted in significant attention on neuroimaging markers so that today cSVD is mainly diagnosed and identified through neuroimaging, mostly magnetic resonance imaging (MRI), rather than clinically.[6] One of the reasons for this is that neuroimaging has become widely available although it is not specific. Considering specificity, great efforts have been made in the last decade to standardize and harmonize neuroimaging aspects of cSVD.[6] On the other hand, the clinical profile of cSVD has received less attention and remains incompletely elucidated. This is particularly true for the cognitive profile of cSVD patients.

Generally speaking, cognitive assessment has both the potential to establish the presence and degree of cognitive impairment (diagnostic value) and to identify the underlying disease process (differential diagnostic value).[7] The use of neuropsychological findings to characterize the clinical profiles of different dementing conditions could be a cost-effective screening strategy, particularly if disease-specific therapeutic approaches become available.

In the last decades, some efforts have been made to identify a pool of cognitive tests to be used as a reference standard in vascular cognitive impairment.[8] The recommendations were based on a priori selection of the appropriate tests according to the expected cognitive profile, for example, their specificity for attention and executive abilities. However, further data on their clinical utility in terms of diagnostic accuracy are needed. As a result, despite the availability of several screening and second-level tests to detect specific cognitive domain deficits, there is no definite agreement on which neuropsychological tools are the most appropriate to outline the pattern of cognitive deficits characteristic of cSVD.

Considering both the impact of cSVD on cognition and the role of neuropsychological assessment in outlining a clinical profile, we explored the possibility of identifying a cognitive marker for cSVD. In particular, we aimed to evaluate whether cognitive test measures recommended and used to assess individuals with cSVD actually discriminate these individuals from cognitively unimpaired and patients with different dementing conditions, and the association of these cognitive tests with neuroimaging markers of cSVD.

To evaluate if available literature could reliably answer our question, we developed a two-phase project designed according to an evidence-based clinical approach. In phase 1, we conducted a systematic review and identified the eight neuropsychological tests most used in cSVD: Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Trail Making Test (TMT) Parts A and B, Stroop Test, phonemic and semantic fluencies, and Boston Naming Test.[9] In this review, we included papers on cSVD when the study reported on patients with lacunar/subcortical infarcts, white matter lesions, lacunar stroke, or different combinations thereof, or with one genetic cSVD form (CADASIL). The present meta-analysis represents the second phase of the project and aims at exploring if the selected neuropsychological tests may be able to detect the pattern of cognitive deficits characteristic of cSVD and to distinguish cSVD from other conditions.

RESEARCH IN CONTEXT

1. **Systematic Review**: Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, original articles focused on samples of patients with cerebral small vessel disease (cSVD) evaluated with cognitive tests were searched using PubMed, Scopus, and PsycINFO databases without time restrictions, and the eight most commonly used neuropsychological tools were identified.
2. **Interpretation**: This meta-analysis highlighted that cSVD patients performed worse than healthy controls in all tests, while there is incomplete evidence that a single test could differentiate cSVD patients with cognitive decline from other dementing diseases. We outlined lack of data on the diagnostic accuracy of these tests. Cognitive tests measuring processing speed were those mostly associated with neuroimaging cSVD markers.
3. **Future Directions**: Cognitive tests sensitive to information processing speed seem the most promising to define a cSVD clinical profile, and reaction time tasks could be further tested in cSVD patients. Phonemic verbal fluency showed some differential diagnostic potential to be further explored following a qualitative approach.

1.2 | Are there neuropsychological tests able to differentiate cSVD patients and healthy controls? Diagnostic potential

cSVD signs are often seen on neuroimaging in aged patients, even when cognitive complaints are not reported or remain undetected by general neurological examination. This has led to the question of whether having cSVD signs on neuroimaging without clinical complaints or disturbances is a pathological condition or not, and many clinicians indeed consider minimal cSVD on neuroimaging a reflection of normal aging.

Following these points, we tried to move in the opposite direction, that is, to explore whether the presence of cSVD signs on neuroimaging could be predicted by performance in some specific cognitive tests. This could have a relevant clinical value.

Two previous meta-analyses focused on available data on neuropsychological performances of cSVD patients compared to control groups without cSVD.[10,11] Both these quantitative syntheses demonstrate that individuals with cSVD performed more poorly than controls in all cognitive domains, without a clear difference between executive function and processing speed and the remaining domains.

TABLE 1 Meta-analyses and meta-regressions results by cognitive tests: cSVD patients versus healthy controls

Comparison group		MMSE	MoCA	TMT-A (time)	TMT-B (time)	Stroop (time)	Phonemic fluency	Semantic fluency	Boston Naming Test
Healthy controls	N° studies	20	9	13	14	8	8	4	5
	N° patients	812	548	357	397	206	169	100	115
	N° controls	937	811	278	298	161	188	117	139
	Cohen's d	−.70	−.79	.86	1.27	.79	−.64	−.72	−.53
	95% CI	−.93; −.47	−1.13; −.45	.53; 1.18	.79; 1.75	.27; 1.31	−.86; −.41	−1.22; −.22	−.96; −.09
	P	.001	.001	.001	.001	.003	.001	.004	.017
	Q	87.7	58.6	40.8	97.3	35.9	7.1	7.4	9.2
	I^2	78.3	86.4	70.6	86.6	80.5	1.4	59.3	56.5
	Meta-regression study quality (p)	.252	.259	.269	.155	.006	.448	na	na

Abbreviations: CI, confidence interval; cSVD, cerebral small vessel disease; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; na, not applicable; TMT, Trail Making Test.

In our first series of meta-analyses, we expected to corroborate the evidence of the ability of several neuropsychological tests to differentiate cSVD patients and healthy controls. Differently from previous meta-analyses, we selected only studies that included cSVD patients without a priori diagnosis of cognitive decline. Data on sporadic cSVD and CADASIL were combined.

Among the 86 studies selected, 25 (16 on sporadic cSVD, 9 on CADASIL) were included in comparison analyses. cSVD patients' performances were significantly lower than those of healthy controls in the two tests of global cognitive functioning, that is, MMSE and MoCA (Table 1). Effect size magnitude was large and similar for both tests. Our results confirmed the lack of superiority of the clinical properties of the MoCA compared to MMSE in this patient population, and were in line with previous comparative studies in cerebrovascular disease patients.[12,13]

Performance in all the second-level cognitive tests were significantly worse in cSVD patients compared to healthy controls (Table 1). The highest pooled effect sizes were indeed obtained in cognitive tests sensitive to attention and executive deficits, that is, TMT-A, TMT-B, and Stroop, thus confirming the importance of this domain failure within the cSVD cognitive profile. Of note, for TMT-B the magnitude of effect size was >1, denoting a very large effect.

When we repeated the meta-analyses including only the 16 studies on sporadic cSVD, the pattern of results was comparable, effect sizes for TMT-A, TMT-B, and Stroop further increased, and all tests exceeded the effect size magnitude threshold of 1.

All applicable meta-regression models showed that effect sizes were not influenced by the study quality, thus reducing the risk that heterogeneity might be due to the quality variability, except for the Stroop test (Table 1). Meta-regression for the Stroop test revealed that effect sizes tended to reduce when the quality of the studies increased, but this association was no more significant when we meta-analyzed only studies on sporadic cSVD.

Our results are in line with previous meta-analyses, and confirm that cognitive worsening in cSVD affects all major cognitive domains. Considering that all the selected cognitive tests were able to differentiate cSVD patients from healthy controls, we partially failed in identifying one or a few cognitive tools to be used as a diagnostic marker of cSVD.

Considering feasibility, when the purpose is the distinction between individuals with or without cSVD markers on neuroimaging, the use of a single test of global cognitive functioning could be considered a cost-effective strategy in both research and clinical settings. However, an in-depth analysis of the relative weights of effect sizes highlighted the impact of timed cognitive tests sensitive to information processing speed and executive functions, such as TMT-A, TMT-B, and Stroop, and these tools would have to be considered the first choice for the identification of cSVD patients by means of a comprehensive neuropsychological assessment.

In conclusion, several neuropsychological tests are able to differentiate cSVD patients and healthy controls, with timed cognitive tests sensitive to processing speed and executive functions as the most promising cognitive markers.

1.3 | Are there neuropsychological tests able to distinguish cSVD from neurodegenerative patients? Differential diagnostic potential

The characterization of cognitive changes that occur during either the prodromal or overt phases of dementias has been the topic of several research efforts, and some typical cognitive profiles have been identified. For example, in Alzheimer's disease (AD), episodic memory is recognized as the earliest and main affected domain, while attentional dysexecutive syndrome is considered the first cognitive manifestation in cSVD.

Only one previous meta-analysis explored differences in neuropsychological performance between cSVD and degenerative MCI patients.[10] The results showed a cognitive profile consistent with common knowledge: vascular MCI patients showed greater deficits in processing speed and executive functions, while degenerative MCI had a greater deficit in delayed memory. Vasquez et al. meta-analyzed data grouping tests performances within cognitive domains, but some results concerning single tests can be extrapolated from their meta-analysis.[10] Within the processing speed domain, TMT-A was significantly underperformed by vascular MCI compared to degenerative only in two of the eight meta-analyzed studies. Similarly, in the executive functions domain, TMT-B, Stroop, and phonemic fluency were significantly worse in vascular MCI in 3 of 10, 2 of 6, and 2 of 13 studies, respectively.[10]

In our second series of meta-analyses, we further tested the hypothesis that there could be some neuropsychological tests able to distinguish cSVD patients from neurodegenerative ones, with particular interest in tools pertaining to attention and executive functions domain.

Fifty-six studies included in this meta-analysis offered data on comparisons between cSVD patients and different dementing conditions. AD and MCI prodromal of AD were the most common comparison groups, with 39 and 13 studies, respectively. Meta-analyzable data were mainly based on MMSE performances (37 studies), no meta-analyzable data was available for MoCA, and data for the second-level tests were very limited.

MMSE scores showed that demented cSVD patients outperformed both AD and Lewy body dementia (LBD) patients, while no significant differences were found for comparisons to the behavioral variant of frontotemporal dementia (bvFTD) and Parkinson's disease dementia (PD), or for vascular versus degenerative MCI (Table 2). As shown in Table 2, among the second-level tests, only phonemic fluency scores were significantly worse in demented cSVD patients compared to AD. Comparing MCI subtypes, the performances of Stroop test and phonemic fluency were significantly worse in vascular compared to degenerative MCI. In applicable meta-regression models, study quality was not associated with effect sizes (Table 2).

In summary, despite a quite large number of studies aimed at identifying cognitive profiles distinctive of cSVD patients compared to neurodegenerative ones, meta-analyzable data were scarce and not all selected tests could be compared across clinical populations of different etiologies.

As expected, MMSE was confirmed as a tool sensitive to neurodegenerative cognitive decline, mainly in overt dementia. MMSE has been the most used test for global cognitive functioning in dementia worldwide, and our data confirmed that it has been extensively used also in studies on cSVD. This supremacy is still unbeaten, and, at present, it is not possible to examine pooled data on MoCA efficacy in differentiating cognitive decline due to cSVD or due to degenerative mechanisms. The increasing interest that MoCA recently obtained in the field of cerebrovascular diseases could lead to meta-analyzable data and further evidence in the near future.

Overall, phonemic fluency was the only test that showed a consistent performance decrease in cSVD cognitively impaired patients compared to neurodegenerative ones. Its potential efficacy in distinguishing cSVD and neurodegenerative patients seemed to decrease going from overt dementia to prodromal phases, and it was not confirmed compared to bvFTD, whose cognitive profile is mainly dysexecutive as in cSVD. Future research efforts should focus on the differential diagnostic potential of phonemic fluency, keeping in mind the above-mentioned limitations, and we are convinced that a qualitative analysis of performances in this test could add useful information. Clustering and switching strategies and time course of both correct responses and errors are qualitative features that have already shown some potential in discriminating across patient populations, and this field of research should be further improved.[14]

In conclusion, there is inadequate evidence that a single test could distinguish cSVD from neurodegenerative patients, but phonemic verbal fluency may have some differential diagnostic potential to be further explored.

1.4 | Are there neuropsychological tests associated with the cSVD neuroimaging markers?

Neuroimaging abnormalities, such as white matter lesions, lacunes of presumed vascular origin, cerebral microbleeds, and perivascular spaces, are the main in vivo markers of cSVD.[6] The association between these markers, particularly white matter hyperintensities, and cognitive performances has been often studied.

Two previous meta-analyses have synthesized evidence on the cognitive correlates of white matter abnormalities in adults without dementia, focusing either on cognitive domains or cognitive tests.[15,16] Gunning-Dixon and Raz found that white matter abnormalities were associated with reduced performance on tasks of global cognitive functioning, processing speed, executive functions, and, to a lesser extent, immediate and delayed memory.[15] Considering single tests, Oosterman et al. found that white matter hyperintensities were associated with reduced performance only on timed executive functions tests, such as TMT-A, Stroop, verbal fluencies, and Digit Symbol Substitution, thus increasing the interest in speed relevance in mental processing in cSVD patients.[16]

Out of the 86 studies that we selected, 12 (7 on sporadic cSVD, 5 on CADASIL) were included in our third series of meta-analyses aimed at evaluating the association between neuropsychological tests and cSVD neuroimaging markers. We hypothesized a stronger association with tools sensitive to attention and executive abilities. Most studies ($n = 11$) took into consideration white matter lesions, while few studies were available for cerebral microbleeds ($n = 2$) and lacunes ($n = 4$), and none for perivascular spaces.

As shown in Table 3, the few meta-analyzable data showed significant but moderate associations between MMSE and white matter lesion volume, number of cerebral microbleeds and lacunes, that is, MMSE worsened along with increasing severity of neuroimaging

TABLE 2 Meta-analyses and meta-regressions results by cognitive tests: cSVD patients with cognitive impairment vs. neurodegenerative patients

Comparison group		MMSE	MoCA	TMT-A (time)	TMT-B (time)	Stroop (time)	Phonemic fluency	Semantic fluency	Boston Naming Test
AD	N° studies	37	1	3	3	0	16	9	8
	N° patients	1210		83	83		468	282	216
	N° controls	1668		123	123		545	313	271
	Cohen's d	.26		.12	.15		−.67	−.12	.31
	95% CI	.13; .39		−.36; .60	−.30; .60		−.90; −.44	−.32; .08	−.01; .63
	P	.001		.619	.515		.001	.230	.057
	Q	100.6		44.2	5.12		44.2	11.5	20.2
	I^2	64.2		66.1	60.9		66.1	30.3	65.3
	Meta-regression study quality (p)	.080		Na	na		.580	.541	.906
MCI prodromal of AD	N° studies	13	1	1	0	3	5	3	3
	N° patients	498				133	181	96	104
	N° controls	434				105	160	90	85
	Cohen's d	.14				.27	−.47	−.02	−.29
	95% CI	.00; .27				.01; .53	−.89; −.04	−.31; .27	−.58; .00
	P	.057				.040	.032	.880	.050
	Q	10.2				0.9	14.2	1.9	0.6
	I^2	0				0	71.8	0	0
	Meta-regression study quality (p)	.340				na	na	na	na

Abbreviations: AD, Alzheimer's disease; CI, confidence interval; cSVD, cerebral small vessel disease; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; na, not applicable; TMT, Trail Making Test.

markers. A significant association between TMT-B and white matter lesion volume or lacunes was also found.

Taking into consideration correlation coefficients from single studies, a strong relationship between TMT-B and visually rated white matter lesions was found in one study, and a similar pattern was reported for the association between TMT-A and white matter lesions evaluated either visually or volumetrically.[17,18] Furthermore, a highly positive association was found in one study between execution time at Stroop test and number of lacunes.[19] Considering phonemic fluency, only one study examined the correlation between performance on the test and volume of white matter lesions finding no association.[17]

Among the considered neuropsychological tests, data on the association between MRI markers and cognitive performance seemed to bring our attention again to timed executive tests, in line with the results obtained by Oosterman et al.[16] Considering the paucity of meta-analyzable data, evidence from this third series of meta-analyses has to be taken with caution, but apparently they reinforce the role of TMT as a test sensitive to the decreased speed of mental processing that is widely considered one of the main hallmarks of the cSVD cognitive profile.

In conclusion, research concerning correlation between neuroimaging markers of cSVD and cognitive tests is still preliminary. In this regard, timed executive tests seem to be highly associated with cSVD biomarkers and the most promising tools.

1.5 | Limitations and strengths

Our meta-analysis has some limitations. First, we found an overall high degree of heterogeneity across studies, and several studies were based on small samples. Random effects models were used to incorporate heterogeneity among studies in meta-analyses, and meta-regression models were applied to verify the overall impact of study quality on effect sizes. However, study quality evaluation reached only a moderate level of inter-rater agreement, and a re-evaluation by consensus was needed for half of the studies. Furthermore, each single potential clinical (e.g., differences in populations) or methodological (e.g., study design or data analysis methods) source of bias was not specifically explored. We attempted to minimize clinical heterogeneity due to patients' selection by only including studies making the cSVD diagnosis with explicit description of cerebral lesion types or referral to international reference standards, but the interpretation of the criteria may nonetheless vary between clinicians. Second, no correction for multiple comparisons was applied in our meta-analyses. To the best of our knowledge, the reliability of using meta-analyses in some of the

TABLE 3 Meta-analyses by cognitive tests: Association with the cSVD neuroimaging markers

Neuroimaging marker		MMSE	MoCA	TMT-A (time)	TMT-B (time)	Stroop (time)	Phonemic fluency	Semantic fluency	Boston Naming Test
WMH visually rated	N° studies	*1*	0	*1*	*1*	0	0	0	*1*
	N° patients	*92*		*40*	*40*				*–.04*
	r	*–.21*		*.72*	*.82*				*42*
	95% CI								
	P	*.037*		*.001*	*.001*				*.817*
	Q								
	I^2								
WMH volume	N° studies	5	*1*	*1*	3	*1*	*1*	0	2
	N° patients	217	*56*	*26*	105	*39*	*26*		68
	r	–.26	*–.47*	*.71*	.31	*.33*	*–.34*		–.22
	95% CI	–.43; –.09			.12; .49				–.49; .06
	P	.003	*.001*	*.001*	.001	*.026*	*.065*		.121
	Q	7			1.9				1.3
	I^2	42.9			0				23.1
Lacunes (number)	N° studies	3	0	0	2	*1*	0	0	*1*
	N° patients	136			80	*40*			*42*
	r	–.40			.62	*.42*			*–.11*
	95% CI	–.69; –.12			.11; 1.14				
	P	.006			.018	*.002*			*.495*
	Q	7.6			13.6				
	I^2	73.5			92.7				
Cerebral microbleeds (number)	N° studies	2	0	0	*1*	*1*	0	0	0
	N° patients	188			*40*	*40*			
	r	–.22			*.13*	*–.13*			
	95% CI	–.38; –.06							
	P	.007			*.421*	*.421*			
	Q	0							
	I^2	0							

Abbreviations: CI, condidence interval; cSVD, cerebral small vessel disease; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; TMT, Trail Making Test; WMH, white matter hyperintensities.
Results from single not meta-analyzable studies are reported in italics.

existing methods to deal with multiplicity in single studies is still under debate.[20,21] Third, some of the labels used for the identification of the comparison groups (e.g., degenerative MCI) and of the neuroimaging markers of cSVD (e.g., white matter alterations) were broad, as the definitions across studies were heterogeneous. Fourth, although we tried to exclude studies on the same cohorts, we cannot be completely sure that the same patients were included in different papers. Fifth, our meta-analyses were limited to the eight neuropsychological tests that were most commonly used in cSVD according to a previous systematic review,[9] and we are aware that frequency of use does not correspond per se to good clinimetric and psychometric properties. As a consequence, some of the potentially eligible cognitive tools recommended in the National Institute of Neurological Disorders and Stroke (NINDS) and Canadian Stroke Network (CSN) harmonization standards for vascular cognitive impairment were not included.[8] Another limitation is related to the fact that the search of the original articles to be included

in the systematic review (the first part of this project) was done in February 2018, and thus some recent studies may be excluded from the present meta-analyses. An additional possible caveat to be outlined in our study was the fact that we included in the meta-analysis studies in which MMSE was an inclusion criterion to assess the presence of cognitive impairment adopting a more conservative approach, excluding only those in which the authors reported to have matched patients at study entry by MMSE scores. Finally, despite being aware of the methodological implications, we decided to explore aggregated data even when available studies were very limited, and to perform meta-analyses also on two to three studies in an exploratory fashion.

Considering generalizability of our results, inherent constraints of the meta-analytical approach also must be considered. Meta-analysis results provide a hint within a likely complex picture of putative associations between promising variables of interest and could yield incomplete or inaccurate delineation of the true phenomenon. Merely relying on recurring findings in previous publication, our results are intrinsically bound by the potential flaws in assumptions, methodology, quality control, and other sources of variance of published studies. Consequently, our preliminary findings are aimed at building some hypothesis to be further tested and validated in future studies.

Strengths of this meta-analysis included a comprehensive search approach, and a methodological effort to ensure groups' comparability for the presence and degree of cognitive impairment. We included, in fact, all studies that reported data on the cSVD patients' performances in the selected cognitive tests, even if this was not the primary aim of the study. This strategy allowed both to increase the number of studies and to include correlations with MRI markers in our analyses together with group comparisons. Moreover, in the comparisons between cSVD patients and healthy controls, we decided to include only studies based on cSVD patients without a diagnosis of cognitive decline to fulfill a ceteris paribus assumption.

1.6 | Summary of results, clinical implications, and future directions

Results from the present meta-analyses highlighted that on all the selected tests, cSVD patients perform worse than healthy controls, while there is incomplete evidence that a single test could differentiate cSVD patients with cognitive decline from other dementing diseases.

In comparison analyses with healthy controls, the highest pooled effect sizes were obtained in timed cognitive tests sensitive to executive domain deficits, confirming the importance of this domain within the cSVD cognitive profile. Despite the paucity of data, this evidence was corroborated also by results on the association between white matter lesions and cognitive performance. Cognitive tools sensitive to the decrease in speed of mental processing can be considered the most promising to define a clinical profile of cSVD. In 2006, the harmonization standards for vascular cognitive impairment of the NINDS and CSN already suggested the inclusion of simple and choice reaction time tasks as additions to the neuropsychological protocol, but few efforts have been made in following years in this direction.[8] The use of new technologies for adapting or creating cognitive tools is growing, and this could represent an ideal framework for the development of reaction time tasks to be tested in cSVD patients.

Despite several research efforts having been made to identify cognitive profiles distinctive of different dementing conditions, meta-analyzable data were limited. As expected, most studies compared cognitively impaired cSVD to AD or MCI prodromal of AD patients. Furthermore, the studies we selected were designed to compare means and standard deviations of cognitive test scores among different patient populations and did not evaluate their diagnostic accuracy. As a result, evidence on the clinical utility of the proposed tests in terms of differential diagnostic potential was inconclusive. However, phonemic verbal fluency was consistently lower in patients with cSVD compared to degenerative ones. Considering the ease of administration of verbal fluency tests, an effort toward an in-depth examination of strategies, errors, and time course of performances could be time and cost effective. Promising evidence already exists on the potential of qualitative features of cognitive performances in discriminating across patient populations; this approach is likely of relevance for future research efforts in this field.[14]

The present meta-analysis was driven by the idea that an evidence-based approach was needed to highlight how to evaluate and distinguish cSVD patients by means of cognitive tests, and represents a novel contribution that may consolidate our knowledge in this field. Our results clearly pointed out the need to address some recurrent methodological shortcomings in future work. Sample sizes, and heterogeneity of cognitive diagnostic criteria and neuroimaging marker definitions emerged as the main constraints of available literature. In designing future studies, the use of the available international reference standards for both SVD and vascular cognitive impairment diagnoses would contribute to reduce heterogeneity.[6,8,22] Moreover, the adoption of a common methodological framework would allow the creation of large international datasets, and for example the use of artificial intelligence methods of analysis, for example, deep and machine learning, able to take into account the multifactorial nature of the phenomenon.

Although preliminary, results concerning both timed cognitive tests and phonemic fluency tests in differentiating cSVD from other populations are promising, and more efforts should be made to correlate test performance with neuroimaging biomarkers of cSVD. As it stands, we can consider refining our cognitive tools focusing on speed and qualitative components of cognitive performances, but no single test can be recommended as a cognitive marker of cSVD.

2 | CONSOLIDATED RESULTS AND STUDY DESIGN

2.1 | Methods

In a previously published systematic review we described in detail the search strategy and selection of studies of phase 1 of the study.[9]

In this systematic review, we focused on the neuropsychological tests most commonly used in cSVD according to our previous review:

TABLE 4 Items included in the 8-item version of the National Institutes of Health Quality Assessment Tool for observational cohort and cross-sectional studies, and distributions of responses

Items	Yes	No	Not reported
Was the research question or objective in this paper clearly stated?	81%	19%	0%
Was the study population clearly specified and defined?	86%	14%	0%
Was the participation rate of eligible persons at least 50%?	18%	6%	76%
Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	78%	22%	0%
Was a sample size justification, power description, or variance and effect estimates provided?	7%	93%	0%
Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	73%	27%	0%
Were the outcome assessors blinded to the exposure status of participants?	10.5%	8%	81.5%
Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	73%	27%	0%

MMSE, MoCA, TMT-A and -B, Stroop test, phonemic and semantic fluencies, and Boston Naming Test. Among studies included in phase 1, we selected only those that applied at least one of the targeted tests, and excluded those with incomplete statistical data or uncertain definition of cSVD patients.

2.2 | Data extraction

Meta-analysis was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and registered on PROSPERO database (ID: CRD42018089882).[23] Four independent reviewers (ES, MB, AN, GM) extracted data from the studies into a standardized form created in ProMeta 3.0 software.

2.3 | Study quality assessment

Study quality was assessed by means of an adapted 8-item version of the National Institutes of Health (NIH) Quality Assessment Tool by two independent raters (ES and GM) (Table 4). A summary table of the ratings was constructed with the two reviewers resolving disagreements by consensus.

2.4 | Statistical analysis

Statistical analyses were conducted with the meta-analytic software ProMeta 3.0. Meta-analytic method was used to synthesize study data: we computed pooled effect sizes (ES) with the inverse-variance method using Cohen's d statistic when available data from primary studies were means and standard deviations, and by means of pooled Pearson's r when original data were correlation coefficients. Conventionally, small ES correspond to values of Cohen's d ≈.20 and Pearson's r ≈.20, medium effect sizes to Cohen's d ≈.50 and Pearson's r ≈.30, large effect sizes to Cohen's d > .80 and Pearson's r > .50.[24,25] For each ES, 95% confidence interval, variance, standard error, and statistical significance were computed. We used the random-effects model as it is a conservative approach useful to account for different sources of variation among studies. Q and I^2 indexes were computed to assess the heterogeneity among the studies.

Several separate random effects meta-analyses were carried out to examine differences between cSVD patients and controls or clinical groups in performances on cognitive tests. Compared to healthy controls, data on sporadic cSVD and CADASIL were pooled. Cognitively impaired cSVD patients, either vascular MCI (vMCI) or subcortical ischemic vascular dementia (SIVD), were compared to clinical groups such as degenerative MCI (dMCI), AD, bvFTD, and LBD.

Meta-regression models were also performed to evaluate if quality of the study influenced the study findings in terms of effect size. Following the recommendation from the Cochrane Statistical Methods Group, we performed meta-regressions when there were at least eight studies in a meta-analysis.[26]

2.5 | Results

2.5.1 | Study selection

Figure 1 shows the flow diagram based on the PRISMA statement. Among the 298 studies previously included in the systematic review, 276 (95%) applied at least one of the eight most commonly used

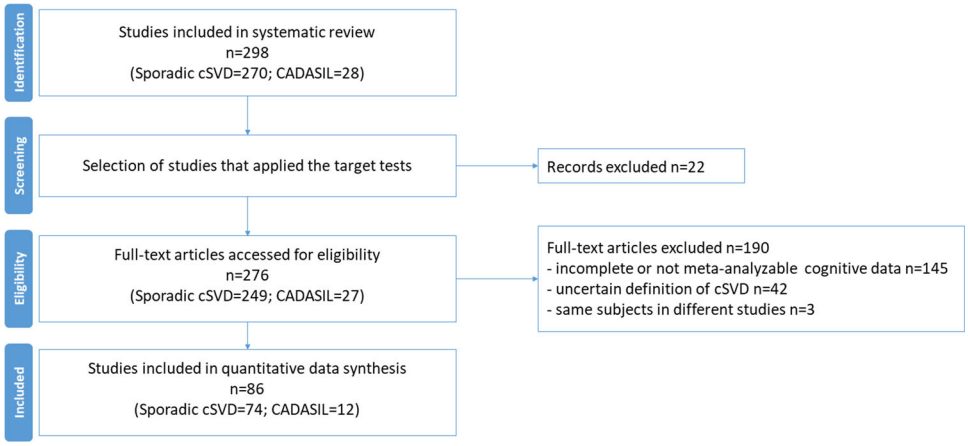

FIGURE 1 Flow diagram. CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; cSVD, cerebral small vessel disease

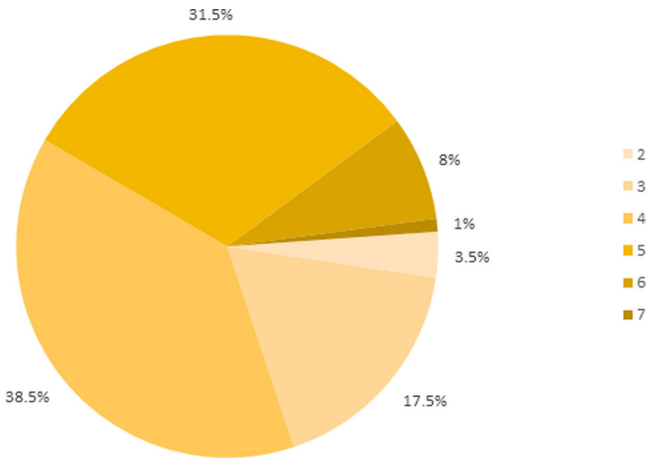

FIGURE 2 Distribution of quality scores in the examined studies

cognitive tests, and 86 (29%) were eligible for the meta-analysis. Two studies were excluded from the analysis of MMSE comparison between vascular dementia and AD because they reported to have matched patients at entry also by MMSE[27,28] although details about matching were not available.

Considering study quality, 68 (79%) studies obtained an NIH Quality Assessment score ≥4 (score range 0–8, median 4; Table 4 and Figure 2).

2.5.2 | Comparison of test performances in cSVD, healthy controls, and patients with neurodegenerative conditions

Compared to healthy controls, cSVD patient scores were significantly lower in both MMSE (d = −.70, 95% confidence interval [CI: −.93; −.47], n = 1749) and MoCA (d = −.79, 95% CI [−1.13; −.45], n = 1359; Table 1 and Figure 3). In comparisons with neurodegenerative patients, cSVD patients with dementia performed better than AD (d = .26, 95% CI [.13; .39], n = 2878) and LBD (d = .34, 95% CI [.06; .62], n = 209) on the MMSE (Table 2 and Figure 4). Considering attention and executive functions tests, TMT-A (d = .86, 95% CI [.53; 1.18], n = 635), TMT-B (d = 1.27, 95% CI [.79; 1.75], n = 695) and Stroop (d = .79, 95% CI [.27; 1.31], n = 367) execution times were significantly higher in cSVD patients compared to healthy controls, and pooled effect sizes ranged from large to very large (Table 1 and Figure 3). No differences were found between cSVD and AD patients in TMT-A and TMT-B. Stroop (d = .27, 95% CI [.01; .53], n = 238) performance was significantly worse in vMCI compared to dMCI (Table 2 and Figure 5). Phonemic fluency scores were significantly lower in cSVD patients compared to healthy controls (d = −.64, 95% CI [−.86; −.41], n = 357), vMCI compared to dMCI (d = −.47, 95% CI [−.89 −.04], n = 341), and cSVD compared to AD (d = −.67, 95% CI [−.90; −.44], n = 1013), with medium to large effects sizes. Both semantic fluency (d = −.72, 95% CI [−1.22; −.22], n = 217) and Boston Naming Test (d = −.53, 95% CI [−.96; −.09], n = 254) performances were significantly worse in cSVD patients compared to healthy controls, while no differences were found between clinical groups.

No association between effect sizes and study quality was highlighted by meta-regression models, except for a significant indirect association when Stroop test performances were compared between cSVD and healthy controls (Table 1). This association was no more significant when we meta-analyzed only studies on sporadic cSVD, thus excluding CADASIL.

2.5.3 | cSVD and neuroimaging markers

We included 13 studies aimed at evaluating the association between cognitive tests and cSVD neuroimaging markers (white matter lesions [n = 11], microbleeds [n = 2], lacunes [n = 4]).

We found significant associations between the global score of MMSE and white matter lesion volume (r = −.26, 95% CI [−.43; −.09], n = 217), number of cerebral microbleeds (r = −.40, 95% CI [−.69; −.12], n = 136) and lacunes (r = −.22, 95% CI [−.38; −.06], n = 188). Significant associations between TMT-B execution time and white matter lesion volume (r = .31, 95% CI [.12; .49], n = 105) and number of lacunes was also found (r = .62, 95% CI [.11; 1.14], n = 80;Table 3).

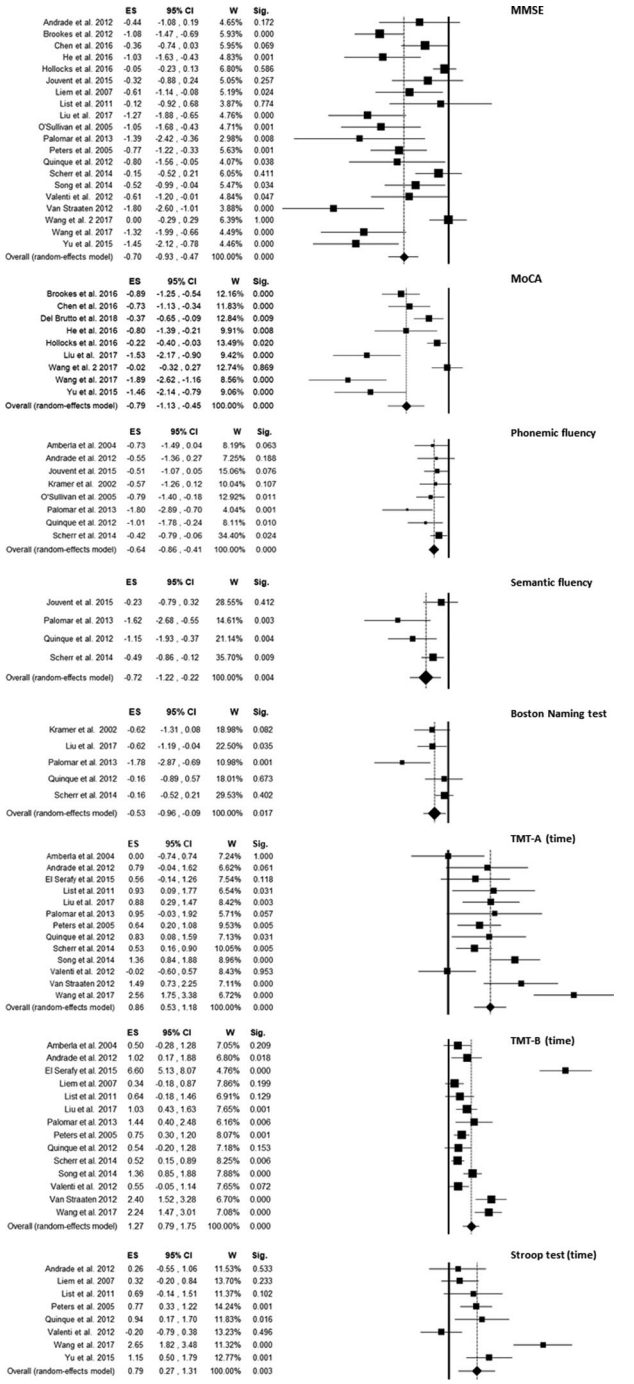

FIGURE 3 Forest plots of meta-analyses comparing cSVD patients versus healthy controls. CI, confidence interval; cSVD, cerebral small vessel disease; ES, effect size; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; TMT, Trail Making Test

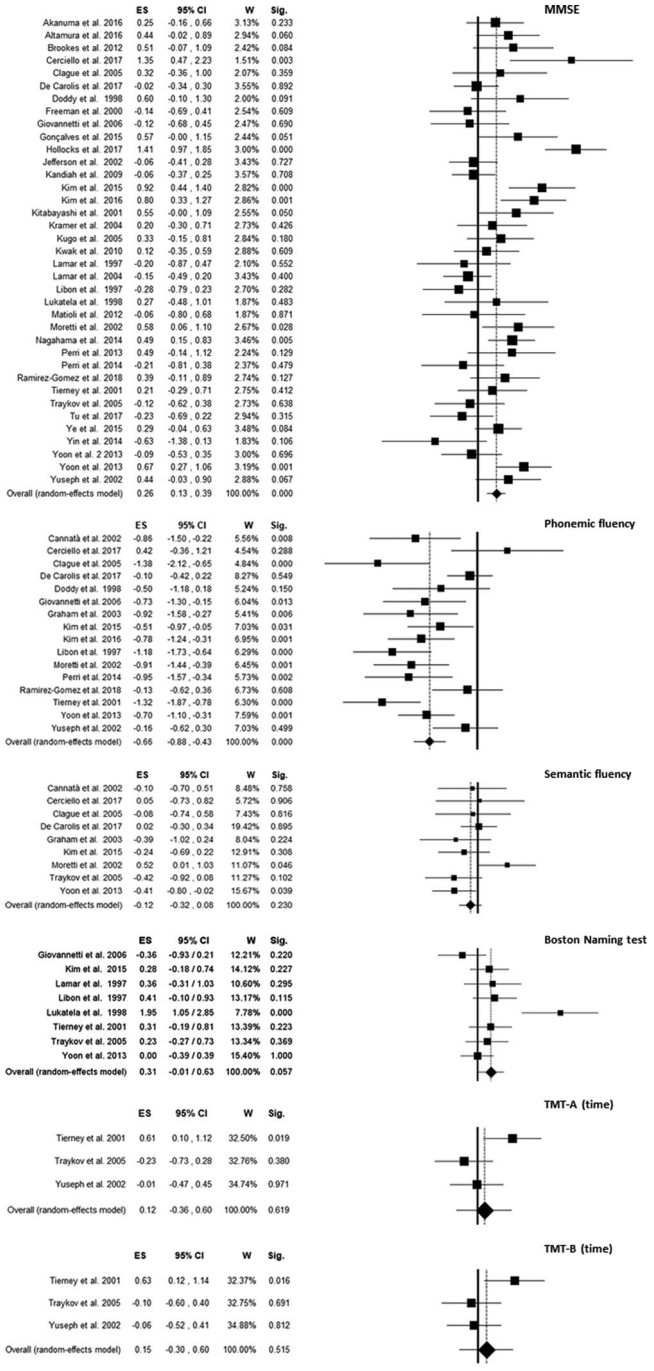

FIGURE 4 Forest plots of meta-analyses comparing cSVD patients with dementia versus AD patients. AD, Alzheimer's disease; CI, confidence interval; cSVD, cerebral small vessel disease; ES, effect size; MMSE, Mini-Mental State Examination; TMT, Trail Making Test

3 | DETAILED METHODS AND RESULTS

3.1 | Methods

The study was conducted in accordance with PRISMA guidelines and registered on PROSPERO database (ID: CRD42018089882, date 27-02-2018).[23]

3.2 | Search strategy and selection criteria

This meta-analysis represents the second part of a project whose aim was to identify neuropsychological protocols and/or batteries specifically developed, used and/or recommended in cSVD.[9]

In the first part, a systematic review was conducted searching original articles using PubMed, Scopus, and PsycINFO from their

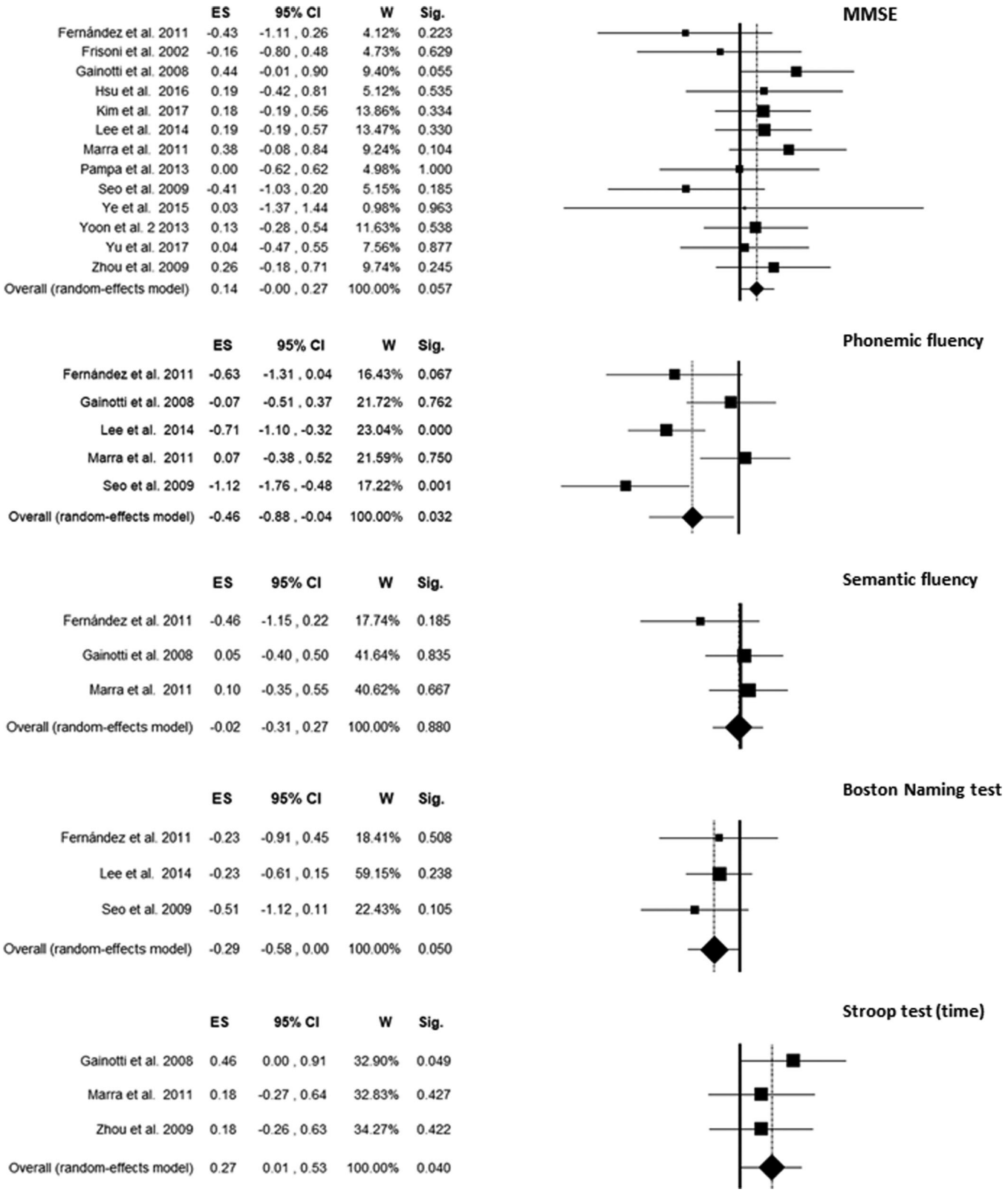

FIGURE 5 Forest plots of meta-analyses comparing cSVD patients with MCI versus MCI prodromal of AD. AD, Alzheimer's disease; CI, confidence interval; cSVD, cerebral small vessel disease; ES, effect size; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; TMT, Trail Making Test patients

respective dates of inception up to February 2018. A targeted search was conducted based on predefined terms and using various Boolean terms to build several algorithms. The search identified the following key concept combinations, which can be summarized as follows: ([Subcortical ischemic cerebrovascular disease] OR [Vascular cognitive impairment] OR [Small vessel disease] AND [neuropsychological evaluation] OR [neuropsychological tests] OR [perceptual disorders] OR [attention] OR [memory] OR [language] OR [executive function]). Full texts of selected articles were reviewed and those articles meeting the inclusion/exclusion criteria were included in the systematic review. Among 13688 studies, 298 papers were included in the qualitative data synthesis (sporadic cSVD n = 270, CADASIL n = 28). The neuropsychological protocols and tools most commonly used to evaluate cSVD patient samples were: MMSE and MoCA as screening tests; and phonemic and semantic fluency, TMT-A and -B, Stroop test, and Boston Naming Test as second-level tests.[9]

In this second part of the project, the full texts of the 298 papers previously identified were reviewed and those articles meeting the inclusion/exclusion criteria were included in the meta-analysis. Inclusion criteria were: (1) cross-sectional, longitudinal, or case-control studies that included at least one previously identified neuropsychological tests (i.e., MMSE, MoCA, phonemic and semantic fluency, TMT-A, TMT-B, Stroop test, and Boston Naming Test); (2) sample size clearly identifiable as having cSVD as defined by: presence of lacunar and/or subcortical infarcts, white matter lesions, lacunar stroke or different combination thereof, or with one genetic cSVD form (CADASIL), and absence of cortical stroke. Exclusion criteria were: (1) incomplete or not meta-analyzable data on neuropsychological tests scores (e.g., scores at neuropsychological tests expressed as median and/or range); (2) not clearly identifiable cSVD population. We further excluded studies that presented results on the same sample size previously analyzed in other included studies, and controlled matching criteria in studies that selected patients at study entry based on MMSE (supplementary information).

3.3 | Comparison groups and correlations

We identified three different groups of cSVD patients according to presence and severity of cognitive impairment. Each category was compared only to groups characterized by the same level of cognitive impairment: (1) cSVD patients (both sporadic cSVD and CADASIL) without an obvious cognitive decline diagnosis were compared to healthy controls; (2) MCI patients with cSVD were compared to degenerative MCI; (3) cSVD with dementia were compared to AD, LBD, mixed dementia, PD, and bvFTD.

Furthermore, we analyzed studies considering correlation between scores on neuropsychological tests and the following neuroimaging features: (1) white matter alterations evaluated either visually, volumetrically, or by means of diffusion tensor imaging indexes (mean diffusivity [MD] and fractional anisotropy [FA]); (2) number of cerebral microbleeds (MB); (3) number of lacunes.

3.4 | Data extraction

Four independent authors (ES, MB, AN, and GM) pulled out key information. In studies concerning comparison between different groups, data of interest were sample size and scores obtained at targeted neuropsychological tests in both cSVD and control groups. The vast majority of cognitive data were presented as mean and standard deviation (sample size and *P*-value). In one study, scores of cSVD patients were divided into two different subgroups (i.e., Binswanger's disease and lacunar state), and we calculated pooled mean and standard deviation.[29]

In studies regarding imaging data, we extracted correlation coefficients between neuropsychological tests scores and neuroimaging markers of cSVD, sample size, and *P*-value.

We excluded data in which the specific test score was unclear (e.g., when in Stroop eest it was not specified whether the reported scores stood for execution time in word reading, color reading or interference). Different scoring systems of the same test were considered distinct tests. This applies mostly to the different Stroop eest and TMT scoring systems.

3.5 | Study quality assessment

Quality assessment criteria were devised according to the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Eight items of the scale that best adapted to the studies included in the meta-analysis were selected (Table 4). Two raters (ES and GM) independently assessed the quality of included studies. Inter-rater agreement was measured using the intraclass correlation coefficient (ICC). Disagreements were resolved by consensus.

3.6 | Statistical analysis

Forty-one separate random effects meta-analyses were carried out to examine differences between cSVD patients and controls or clinical groups in performances on cognitive tests. Cognitive data were mostly presented as means, standard deviations, and *P*-values and were converted in ES estimates, using Cohen's d statistic. Values of Cohen's $d < .20$ indicate small effects, values of about .50 moderate effects, and values of about .80 large effects.[24,25]

Regarding imaging data, eight separate random effects meta-analyses were carried out to evaluate the presence and strength of associations between MRI measures and cognitive performance. Considering that available data from primary studies were correlation coefficients, we computed pooled Pearson's r and used it as ES estimate. Small ES corresponds to values of Pearson's $r \approx .20$, medium effect sizes to Pearson's $r \approx .30$, large effect sizes to Pearson's $r > .50$.[24,25] We decided to use Pearson's r as ES measure also to compare the magnitude of the associations found by means of the meta-analyses with those extrapolated by single not meta-analyzable studies.

Both in comparison and correlation meta-analysis, data on sporadic cSVD and CADASIL were pooled.

For each ES, 95% CI, variance, standard error, and statistical significance were computed. Furthermore, a weight was assigned to each study with the inverse-variance method. We used the random-effects model for obtaining an overall effect size since it is a conservative approach useful to account for different sources of variation among studies. Heterogeneity among the studies was quantified using the Cochran's Q test and I^2 statistics.

Meta-regression models were also performed to examine the study quality influence on effect size and to assess whether the inclusion of lower quality studies affected the results of the meta-analyses. Following the recommendation from the Cochrane Statistical Methods Group, meta-regressions were performed only when there were at least eight studies in a meta-analysis.[26]

Statistical analyses were performed using the meta-analytic software ProMeta 3.0 (Internovi).

3.7 | Results

3.7.1 | Study selection

Figure 1 shows the PRISMA flow diagram. Out of 298 studies previously included in the systematic review, 22 studies were excluded because they did not include at least one of the targeted neuropsychological tests, 145 studies were removed due to incomplete statistical data for meta-analysis, 42 studies were excluded due to uncertain clinical population, and 3 studies were removed because authors carried out analysis on the same sample previously analyzed in other included studies. Finally, 86 papers were eligible for the analysis. Two studies were excluded from the analysis of MMSE because they reported to have matched patients at study entry also by MMSE (although details about matching were not available).[27,28] Among the 86 studies, 77 (68 sporadic cSVD and 9 CADASIL) compared cSVD and other populations at test performance; 12 (7 sporadic cSVD and 5 CADASIL) examined the correlation between test performance and neuroimaging markers of cSVD.

Among the 86 studies, the ICC resulted in a moderate level of agreement (rho = .442). Disagreement between the two raters in 43 studies was re-evaluated by consensus. Sixty-eight (79%) studies obtained on the modified NIH Quality Assessment Tool a score above the median of 4 (Table 4 and Figure 2).

3.7.2 | Meta-analyses

Twenty-five studies compared cSVD and healthy controls performances at targeted tests (16 sporadic cSVD and 9 CADASIL).[18,19,30–52] Among these studies, 20 compared performances at MMSE; 9 at MoCA; 13 at TMT-A; 14 at TMT-B; 8 at Stroop test; 5 at Boston Naming Test; 8 and 4 at phonemic and semantic fluency, respectively (Table 1 and Figure 3).

cSVD patient performances were significantly lower than healthy controls in both tests of global cognitive functioning: MMSE (d = –.70, 95% CI [–.93; –.47], n = 1749) and MoCA (d = –.79, 95% CI [–1.13; –.45], n = 1359). Considering attention and executive functions tests, TMT-A (d = .86, 95% CI [.53; 1.18], n = 635), TMT-B (d = 1.27, 95% CI [.79; 1.75], n = 695) and Stroop test (d = .79, 95% CI [.27; 1.31], n = 367) execution times were significantly higher in cSVD patients compared to healthy controls (which corresponds to a significantly worse performance of cSVD), and pooled effect sizes ranged from large to very large. Both phonemic (d = –.64, 95% CI [–.86; –.41], n = 357) and semantic (d = –.72, 95% CI [–1.22; –.22], n = 217) fluency scores were significantly lower in cSVD patients compared to healthy controls. Also Boston Naming Test (d = –.53, 95% CI [–.96; –.09[, n = 254) performances were significantly worse in cSVD patients.

Using meta-regression models, only comparison of execution time at Stroop test between cSVD and healthy controls were significantly associated with studies quality. No other association between quality of the studies and effect sizes were found.

Thirty-nine studies compared scores at selected tests in cSVD patients with dementia and AD patients (Table 2 and Figure 4).[27,31,53–89] cSVD patients performed better than AD (d = .26, 95% CI [.13; .39], n = 2878) on the MMSE (37 studies). No significant differences were found between cSVD and AD patients in TMT-A (3 studies), TMT-B (5 studies), semantic fluency (9 studies), and Boston Naming Ttest (8 studies), while phonemic fluency scores (d = –.67, 95% CI [.90; .44], n = 1013) were significantly lower in cSVD patients compared to AD (16 studies).

Thirteen studies analyzed differences in test performances between vascular and degenerative MCI (Table 2 and Figure 5).[85,87,90–100] No significant differences were found on MMSE (13 studies), semantic fluency (3 studies), and Boston Naming Test (3 studies), while Stroop test performance (3 studies; d = .27, 95% CI [.01; .53], n = 238) and phonemic fluency scores (5 studies; d = -.47, 95% CI [–.89; –.04], n = 341) were significantly worse in vascular MCI patients.

Among the seven studies comparing performances between cSVD patients with dementia and bvFTD, no significant difference was found on MMSE (7 studies), phonemic (4 studies), and semantic (3 studies) fluency performances (data not shown).[55,56,70,77,79,80,101] cSVD patients with dementia outperformed LBD (d = .34, 95% CI [.06; .62], n = 209, 3 studies) on the MMSE,[78–80] while no other significant difference was found compared to PDD (3 studies),[59,64,72] mixed dementia (2 studies), and post-stroke dementia (2 studies; data not shown).[29,67,81,102]

Meta-regression models showed no significant association between study quality and effect sizes.

Through meta-analysis, a negative association was found between MMSE and white matter lesions volumes (r = –.26, 95% CI [–.43; –.09], n = 217), number of lacunes (r = –.40, 95% CI [–.69; –.12], n = 136) and number of microbleeds (r = –.22, 95% CI [-.38; –.06], n = 188) in cSVD patients (in, respectively, 5, 3, and 2 studies, Table 3).[17,19,51,103–105] No significant pooled correlation was found between MMSE and white matter hyperintensity diffusion tensor imaging indexes (2 studies, data not shown).[106,107] One single not meta-analyzable study found a high negative correlation between MoCA performance and volumes of

white matter lesions (r = –.47, n = 56).[103] Overall, these results suggest that a worse performance on global cognitive functioning tests can be observed in subjects with a greater presence of cSVD biomarkers, with associations ranging from mild to moderate.

Investigating execution time at TMT-B, one meta-analysis (3 studies) found a high correlation with volumes of white matter lesions (r = .31, 95% CI [.12; .49], n = 105, 3 studies) and number of lacunes (r = .62, 95% CI [.11; 1.14], n = 80, 2 studies; Table 3).[17,19,104] One single not meta-analyzable study found a strong correlation between TMT-B and visual white matter hyperintensity (r = .82, n = 40), and two further studies found strong associations between execution time at TMT-A and visual (r = .72, n = 40) or volumetric (r = .71, n = 26) evaluation of white matter hyperintensities, thus confirming that larger lesions correlate to an increase in the time required to complete these tests.[17,18]

No meta-analyzable data were available for Stroop test and verbal fluencies. Considering execution time at Stroop rest, one study found a moderate association with volumes of white matter lesions (r = .33, n = 39) and a high association with number of lacunes (r = .42, n = 40), but not with number of microbleeds.[19] One study investigated the correlation between scores at phonemic fluency and white matter hyperintensity volume, finding no association.[17] No study examined association between scores at semantic fluency test and cSVD biomarkers.

No pooled significant correlation was found between performance at Boston Naming Test and white matter hyperintensity volume, nor single significant correlations were found in two studies on visual white matter hyperintensity and number of lacunes.[17,108]

CONFLICTS OF INTEREST/DISCLOSURE STATEMENT

Simone Pomati received a grant from the Italian Ministry of Health for a multicenter study evaluating the accuracy of three memory tests for early diagnosis of Alzheimer's Disease. He was the PI of the study. Funding was to the Luigi Sacco University Hospital and SP received no personal money for this study. All the remaining authors report no disclosure. This statement refers to the conflicts of interest of Dr. Simone Pomati, but the present study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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