Review Article

Association Between Silent Brain Infarcts and Cognitive Function: A Systematic Review and Meta-Analysis

Chunyan Lei, MD, PhD, Qionghua Deng, MD, Haijiang Li, MD, and Lianmei Zhong, MD, PhD

Background and Purpose: Silent brain infarct (SBI), which has traditionally been considered clinically silent, has been proposed as a subclinical risk marker for future cognitive function decline. *Methods:* We conducted a systematic review of literature in the Cochrane Library, MEDLINE, EMBASE, and the China National Knowledge Infrastructure database. *Results:* In the end, 19 case-control studies, comprising 6712 participants, and 3 prospective cohort studies comprising 4433 participants, met all inclusion criteria and were included in the systematic review. Meta-analysis of 9 studies showed that SBI was an important factor in cognitive function decline (Mini-Mental State score) (standardized mean difference −.47, 95% confidence interval; −.72 to −.22). Another meta-analysis of 4 studies reported the SBI was an independent factor in cognitive dysfunction (Montreal Cognitive Assessment Scale) (standardized mean difference −3.36, 95% confidence interval; −5.90 to −.82). Ten studies further reported that SBI was associated with decreases in specific areas of cognitive function. *Conclusions:* These results suggest that rather than being clinically silent, SBI might be a factor inducing cognitive dysfunction.

Key Words: Silent brain infarcts—cognitive function—systematic review—meta-analysis

Introduction

Silent brain infarct (SBI) has been recognized as a common lesion, especially in the older population and certain other at-risk populations.[1-3] The overall prevalence of SBI ranges from 8% to 28% in these studies, with the differences mainly explained by age.[1-3] SBI is widely used to describe cerebral infarcts seen on brain computed tomography (CT) or magnetic resonance imaging (MRI) without both local neurologic signs and previous history of infarction or transient ischemic attack.[1-4] In recent years, with major advances in imaging technology, SBI have been studied in any detail. The neuropathological features of SBI are small in size and number, which might be a critical aspect of the disorder's asymptomatic nature. These lesions are not benign and associations with subtle neurological deficits, cognitive dysfunction, and psychiatric disorders.[1-3]

However, the true association between SBI and cognitive function remains controversial, and our understanding of SBI and special domain of cognitive function limited, including learning, memory, attention, language, generalization, and calculation, et al.[1-3] In the Rotterdam Scan Study, which was a prospective, population-based cohort study, showed that elderly people with silent brain infarcts had an increased risk of dementia and a steeper decline in cognitive function than those without such lesions.[5] In addition, other studies indicated that individuals who presented with a high burden of SBI on MRI might be considered for neuropsychological evaluation, even in the absence of evidence of gross neurological dysfunction. Moreover, the study showed that SBI corresponded to poorer executive functioning even in otherwise normal elderly, which was consistent with the hypothesis that SBI preferentially disrupts frontal-subcortical circuits.[6]

From the Department of Neurology, First Affiliated Hospital of Kunming Medical University, Kunming, Yunnan Province, PR China.

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Address correspondence to Lianmei Zhong, MD, PhD, Department of Neurology, First Affiliated Hospital of Kunming Medical University, No. 295 Xi Chang Lu, Kunming 650032, Yunnan Province, PR China. E-mail: 13888967787@163.com.

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Thus, it is necessary that there is systematic review and meta-analysis to study the true association between SBI and cognitive function and SBI and special domain of cognitive function limited, including memory, motor function, visual perception, intelligence, attention, language, and executive function.

Materials and Methods

We restricted this review to clinical studies on SBI and cognitive function. Cochrane systematic review methods were applied as much as possible.

Study Identification

Two reviewers (C.L. and Q.D.) independently identified studies through searches of the Cochrane Library (issue 12, 2016), MEDLINE (1966 to May 2016), EMBASE (1980 to May 2016), and the China National Knowledge Infrastructure database of Chinese biomedical research literature (1999 to May 2016). Reference lists of all relevant articles were also searched for additional studies.

Study Selection

Studies of SBI and cognitive function were eligible. Specific inclusion criteria were: (1) English and Chinese language articles; (2) studies with more than 10 subjects; (3) the age of participant with more than 18 years; (4) participant without nervous and psychiatric system diseases seriously affecting cognitive function. We defined SBI as round or ovoid lesions 3-15 mm in diameter, with hypointensity on T1-weighted images and hyperintensity on T2-weighted images and excluded perivascular spaces.[4]

Studies had to be controlled, with participants divided into the SBI group and non-SBI group. To be eligible, studies had to evaluate either global cognitive function or at least domains of cognitive function separately, including psychomotor speed, fluency, attention, memory, processing speed, executive function, naming, calculation, language, recall, and abstraction. Outcome measures had to include the presence of SBI. Cognitive impairment, which had to be scored according to a widely accepted standardized scale, was defined as statistically significant deterioration in global cognitive function in any domain of cognitive function.

Data Extraction and Study Quality

Two reviewers (C.L. and Q.D.) independently selected studies that met the inclusion criteria and extracted data with disagreements in data extraction resolved by a third reader. The following data were extracted from each study: first author of the study, country of the study, total number of subjects, age of participant, sex of participant, study design (prospective or not), major study inclusion criteria, mean follow-up, the presence and location of SBI, as well as cognitive measures and the nature of any cognitive deficits observed. Missing data were obtained from the authors whenever possible.

We adapted bias assessment criteria used in a previously published meta-analysis.[7] A total of 9 questions were generated to evaluate potential selection, detection, misclassification, reporting, and confounding bias (Table 1). Risks of bias questions were assessed by 2 readers, with disagreements in assessment resolved by a third tie-breaking evaluator. Articles are considered as high quality if the score is more than 5 points.

Data analysis

Results were reported as odds ratios (ORs) with corresponding 95% confidence intervals (CIs) for dichotomous data. The weighted mean difference or standardized mean difference (SMD) was calculated for continuous data. Heterogeneity between study results was assessed using a standard I^2 test. All calculations were carried out using statistical software provided by the Cochrane Collaboration (RevMan 5.3).

Results

Description of Studies

We identified 690 potential studies from our initial electronic databases and 61 potential studies from reference lists, of 69 studies were excluded because of duplication. The full text of the remaining 51 studies was read. Of those studies, 11 studies were excluded because the articles were reviews or commentaries; 4 studies did not meet inclusion criteria as they have less than 10 participants; 13 studies were excluded because the participant had nervous and psychiatric system diseases seriously affecting cognitive function; 4 studies were excluded because the age of participant was less than 18 years (Fig 1). In the end, 19 case-control studies, comprising 6712 participants, and 3 prospective cohort studies comprising 4433 participants, met all inclusion criteria and were included in the systematic review.[5,7-27] The participants in 4 studies were population based.[5,7,21,27] While the participants in 4 studies were community based.[11,15,24,26] The participants in the remaining studies mainly were stroke-free subjects or healthy volunteers.

Study Characteristics

The basic characteristics of the included studies were summarized in Table 2. In 1 study, participants were further divided into clinically recognized stroke (SBI group versus non-SBI group: 170 versus 250) and without prior stroke (SBI group versus non-SBI group: 961 versus 2436).[7] In 1 study, SBI group was divided into subcortical infarct group and cortical infarct group.[15] Mean age varied from 48.6 to 80.0 years. The average length of education, reported in 13 of 19 studies, varied from 4.15 to 13.0 years. All 14 studies were conducted in China,[9,10,12-14,16-20,22-25] 4 in United States,[7,15,26,27] and 1 each in Singapore,[21] Japan,[8] Netherlands,[5] and Germany.[11]

Table 1. *Risk of bias questions to assess the quality of included studies*

Type of bias	Question	Answers
Selection	Was the study sample randomly selected or a community-dwelling population to minimize the risk of selection bias[xx]	Yes (+) or no (-)
	Were the inclusion and exclusion criteria adequately described?	Yes (+) or no (-)
	Was the study's primary objective to assess whether SBI is predictive of all cognitive function or any domain of cognitive function?	Yes (+) or no (-)
Detection	Were the investigators blinded to the clinical history of patients during ascertainment of SBI?	Yes (+) or no (-)
	Did more than one investigator assess for the presence of SBI?	Yes (+) or no (-)
Misclassification	Did the investigators describe a method by which SBI was differentiated from dilated perivascular spaces?	Yes (+) or no (-)
Reporting	Were the investigators blinded to the clinical history of patients during ascertainment of neuropsychological battery?	Yes (+) or no (-)
	Did more than one investigator assess for the presence of neuropsychological battery?	Yes (+) or no (-)
Confounding	Were data adjusted for covariate risk factors to minimize the risk of confounding bias?	Minimal (+) if studies controlled for 3 of the following 6 potential stroke risk factors which are potential confounders: age, sex, education, microbleeds, leukoaraosis, and trophy by including these variables in the multivariate model or by ensuring that patients with and without SBI were similar or matched on these variables. Relatively higher risk (-) if studies did not provide adjusted risk metric demonstrating strength of association between SBI and cognitive function or any domain of cognitive function.

Note if data not provided or not specified, recorded as no (-).

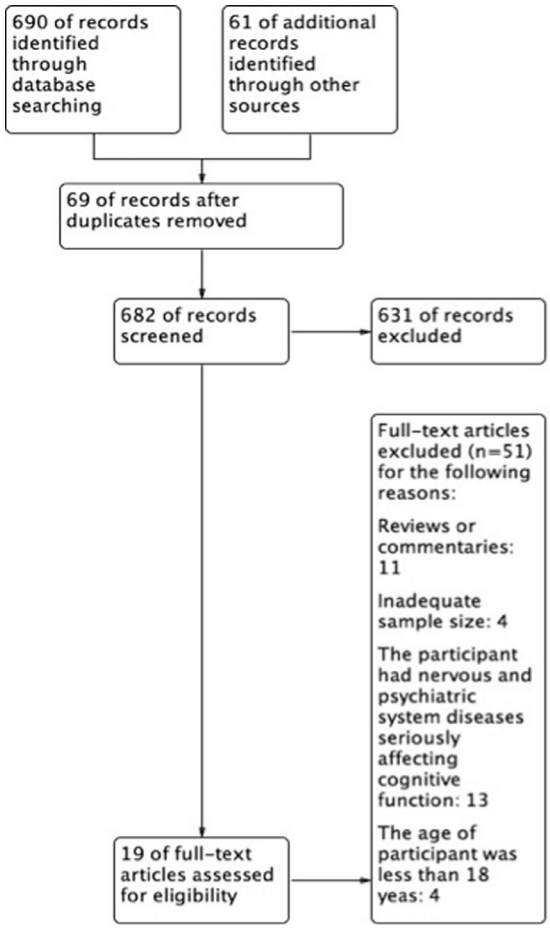

Figure 1. *Flow diagram of the study selection process.*

The Characteristics of SBI

The identification of SBI lesions in magnetic resonance imaging was largely varied across studies. Three types of major criteria were applied: SBI were defined as "hypointense lesions on T1-weighted images (WI) and hyperintense on T2-WI;[5,7,9,11,20,27] (2) only lesions with cerebrospinal fluid (CSF)-like signal intensity were considered as SBI;[15,21,26]] and (3) SBI were defined as round or ovoid lesions of increased signal relative to white matter on T2-WI and T2-fluid-attenuated inversion recovery images or decreased attenuation similar to CSF−filled cavities on T1 images (Table 5).[24] The perivascular spaces were clearly distinguished in 5 studies.[5,7,15,21,26]

Neuropsychological Assessment

The included studies relied on a diversity of neuropsychological assessment (Table 3). Eleven studies used the Mini-Mental State Examination (MMSE);[8,9,11−15,19,20,23,24]; 7 studies used the Montreal Cognitive Assessment Scale (MOCA);[16−20,22,25] 2 study used the modified MMSE.[7,27] These generalized screening instruments assessed global cognitive function, but not function in specific cognitive domains. Twelve studies used a battery of neuropsychological tests to examine specific areas of cognitive function including memory, motor function, visual perception, intelligence, attention, language, and executive function.[5,8,10-15,20,21,24,26]

Study Quality

The results from the quality assessment questionnaire are shown in Table 4. In 4 of the 19 studies, the risk of selection bias was minimized by recruitment from a community-dwelling population.[11,15,24,26] All the studies had the adequate inclusion and exclusion criteria. Three studies involved more than 1 investigator assessing for MRI studies for the presence of SBI and included blinded assessment of SBI lesions.[8,15,27] Six studies showed that perivascular spaces were systematically differentiated from SBI.[5,8,11,15,21,26] Three studies involved more than 1 investigator assessing for neuropsychological assessment.[8,24,25] None of the studies featured blinded neuropsychological assessment. All the studies adjusted for covariate risk factors, such as age, sex, and education to decrease the risk of confounding bias in their analysis. Based on the methodological quality scores, 8 studies were deemed to be of high quality (quality scores≥6), and 13 were categorized as low quality.

Quantitative Analysis of Cognitive Function

Nine studies reported the means and SD of MMSE for SBI and non-SBI groups. Since they showed significant heterogeneity ($I^2 = 73\%$, $P = .002$) reflecting the quite different numbers of participants and high standard deviation (SD) for cognitive function scores, a random-effect model was used. Meta-analysis showed that SBI was an important factor in cognitive function decline (SMD −.47, 95%CI −.72 to −.22) (Fig 2).[8,9,12-15,19,20,24] Another 4 studies reported the means and SD of MOCA for SBI and non-SBI groups. Similarly, 4 studies also indicated significant heterogeneity ($I^2 = 99\%$, $P < .001$). Meta-analysis showed that SBI was an independent factor in cognitive dysfunction (SMD −3.36, 95%CI −5.90 to −.82) (Fig 3).[18-20,25]

Qualitative Analysis of Cognitive Function

We were able to obtain sufficient raw data to calculate a crude OR for cognitive dysfunction in the presence of SBI for 4 studies. In 4 studies, an MOCA score ≥26 was classified as normal, and a score less than 26 was classified as cognitive dysfunction. Data pooled from these 4 studies showed that the OR for cognitive function decline in the SBI group relative to the non-SBI group was 3.08 (95%CI 2.09-4.57) (Fig 4).[16-18,22] Ten studies further reported that SBI was associated with decreases in specific areas of cognitive function including memory, motor function, visual perception, intelligence, attention, language, and executive function (Table 3).[8,10-15,20,21,24]

Table 2. *Characteristics of studies included in the systematic analysis*

Study	Country	N (Male)		Age (years)		Study design		Control (major inclusion criteria)
		Participant	Control	Participant	Control	Type	Follow-up	
Price 1997a	United States	961 (?)	2436 (?)	76.0 ± ?	74.6 ± ?	Cross-sectional	No	Population-based study
Price 1997b	United States	170 (?)	80 (?)	76.7 ± ?	76.1 ± ?	Cross-sectional	No	Population-based study
Maeshima 2002	Japan	21 (8)	63 (30)	49.4 ± 5.6	48.6 ± 5.5	Cross-sectional	No	Subjects with normal nervous system examination; no history of cerebrovascular disease
Li 2003	China	47 (27)	31 (18)	67.19 ± 5.05	65.61 ± 4.51	Cross-sectional	No	Stroke-free subjects or healthy volunteers; no history of neurological and psychiatric diseases
Vermeer 2003	Netherlands	1015 (489)	··	72.1 ± 7.4	··	Cohort study	Median 3.6 years	Population-based study
Zhong 2003	China	112 (59)	50 (27)	61.2 ± 6.1	62.5 ± 7.4	Cross-sectional	No	Stroke-free subjects or healthy volunteers; no history of neurological and psychiatric diseases
Schmidt 2004	Germany	34 (22)	215 (?)	74 ± ?	77 ± ?	Cross-sectional	No	Community-based study
Elkins 2006	United States	1443 (?)	··	?	··	Cohort study	Median 5.0 years	Population-based study
Li 2006	China	128 (128)	38 (38)	73.8 ± 7.1	73.2 ± 6.1	Cross-sectional	No	Stroke-free subjects or healthy volunteers; nervous system diseases seriously affecting cognitive function; severe liver and renal dysfunction
Wang 2008	China	61 (15)	56 (11)	65.7 ± 6.4	63.3 ± 5.7	Cross-sectional	No	Stroke-free subjects or healthy volunteers; no history of tumor; no history of severe liver and renal dysfunction
Debette 2010	United States	1975 (1052)	253 (127)	62 ± 9	65 ± 9	Cohort study	Median 6.2 years	Community-based study
Zhang 2010	China	78 (42)	78 (48)	71.2 ± 5.7	70.4 ± 5.6	Cross-sectional	No	Stroke-free subjects; no history of neurological and psychiatric diseases
Blum 2012a	United States	132 (52)	484 (149)	79.90 ± 5.77	80.09 ± 5.48	Cross-sectional	No	Community-based study
Blum 2012b	United States	42 (16)	484 (149)	79.26 ± 5.78	80.09 ± 5.48	Cross-sectional	No	Community-based study
Wen 2012	China	76 (40)	76 (42)	71.5 ± 6.3	72.4 ± 7.8	Cross-sectional	No	Stroke-free subjects; no history of neurological and psychiatric diseases
Wang 2012	China	101 (58)	70 (38)	65.6 ± 4.7	66.3 ± 4.9	Cross-sectional	No	Stroke-free subjects; no history of psychiatric diseases, intracranial tumors, and Alzheimer disease
Yuan 2012	China	40 (?)	40 (?)	64.2 ± 3.9	63.9 ± 4.1	Cross-sectional	No	Stroke-free subjects; no history of neurological and psychiatric diseases
Zhang 2012	China	68 (36)	62 (30)	58.24 ± 3.56	57.30 ± 3.87	Cross-sectional	No	Stroke-free subjects or healthy volunteers; no history of psychiatric diseases
Fang 2013	China	46 (20)	91 (47)	70.9 ± 6.4	71.4 ± 5.9	Cross-sectional	No	Stroke-free subjects; no history of neurological and psychiatric diseases
Thong 2013	Singapore	34 (17)	251(128)	75.06 ± 6.43	70.49 ± 6.43	Cross-sectional	No	Stroke-free subjects; population-based study
Gao 2013	China	118 (?)	32 (?)	··	··	Cross-sectional	No	Stroke-free subjects; no history of neurological and psychiatric diseases; serious cognitive dysfunction

Table 2 (*Continued*)

Study	Country	N (Male)		Age (years)		Study design		Control (major inclusion criteria)
		Participant	Control	Participant	Control	Type	Follow-up	
Qu 2013	China	59 (32)	50 (28)	61.1 ± 3.2	59.1 ± 3.8	Cross-sectional	No	Stroke-free subjects; no history of neurological and psychiatric diseases
Chen 2015	China	27 (19)	30 (12)	65.81 ± 5.93	63.53 ± 6.11	Cross-sectional	No	Community-based study
Yang 2015	China	62 (34)	62 (34)	52.96 ± 4.16	53.12 ± 3.97	Cross-sectional	No	Stroke-free subjects or healthy volunteers; no history of neurological and psychiatric diseases; no history of alcohol or drug dependency

In Price 1997 study, participants were further divided into clinically recognized stroke (SBI group versus non-SBI group: 170 versus 250) and without prior stroke (SBI group versus non-SBI group: 961 versus 2436).

In Blum 2012 study, SBI group was divided into subcortical infarct group and cortical infarct group.

Qualitative analysis of cognitive function

Because cohort study used different statistical methods to study the relation SBI and cognitive function, meta-analysis was not adopted. Vermeer et al study showed that global cognitive function (adjusted mean difference in z score, −.11; 95% CI, −.20 to −.01) and psychomotor speed (adjusted mean difference in z score, −.19; 95% CI, −.34 to −.04) was significantly worse in participants with silent brain infarcts on the baseline MRI than in those without such infarcts.[5] The presence of silent brain infarcts at baseline was not associated with memory performance (adjusted mean difference in z score, −.01; 95% CI, −.16 to .15) and a decline in the MMSE (adjusted mean difference in z score, -.01; 95% CI, −.44 to .33).[5] Elkins et al study showed that a new MRI-defined infarct was associated with a 3.9-point (95% CI 2.9 to 4.9) decline in digit−symbol substitution test score and a 2.6-point (95% CI 1.7 to 3.5) decline in modified MMSE score, after adjustment for age, race, sex, and education.[27] In Debette et al study, SBI was associated with incident all mild cognitive impairment (OR = .73; 95% CI .35-1.52) or amnestic mild cognitive impairment (OR = 1.26; 95% CI .69 to 2.31).[26]

Location of SBI Lesions and Cognitive Function

One study showed that SBI in domain of the middle cerebral artery was more likely to have global cognitive dysfunction than in domain of the posterior cerebral artery.[22] One study reported that SBI in the subcortical and cortical domains was associated with poorer memory, language, executive function, visuospatial ability, and speed.[15] Another study indicated that the presence of SBI in external capsule was related with auditory verbal learning test-delay recall ($r = .422$; $P = .040$), auditory verbal learning test total ($r = .452$; $P = .027$), and category verbal fluency test ($r = .475$; $P = .019$) after adjusting for age, sex, and education.[24] While 1 study indicated that no obvious tendency that silent brain infarctions in some special location (basal ganglia, thalamus, corona radiate, and brainstem) had more significant effect on cognitive function.[20] SBI in the thalamus were associated with a greater decline in memory performance (Thalamic versus Nonthalamic: adjusted mean difference in z score, −.50; 95% CI, −.87 to −.13 versus adjusted mean difference in z score, .06; 95% CI, −.10 to .23), whereas infarcts located elsewhere resulted in a greater decline in psychomotor speed (Thalamic versus Nonthalamic: adjusted mean difference in z score, −.11; 95% CI, −.36 to .13 versus adjusted mean difference in z score, −.20; 95% CI, −.36 to −.05).[5] The remaining studies did not report a relationship between SBI location and cognitive function.

Table 3. *Psychological tasks or test batteries used and integration and interpretation of test results*

Study	Psychological tasks or test batteries	Nature of deficits	*P* value
Price 1997a	Modified Mini-Mental State score (MMSE)	Global cognitive function	*P*=.0001
Price 1997b	Modified MMSE	Global cognitive function	*P*=.6
Maeshima 2002	MMSE;	Global cognitive function;	$P < .05$;
	Raven's colored progressive matrices (RCPM) test;	Memory;	$P < .05$;
	Word fluency test (WFT);	Language;	$P > .05$;
	auditory-verbal learning test (AVLT);	Language;	$P > .05$;
	''kana-hiroi'' test;	Language;	$P > .05$
Li 2003	MMSE	Global cognitive function	*P*=.397
Vermeer 2003	Neuropsychological tests	Global cognitive function	*NA*
		Memory performance	
		Psychomotor speed	
Zhong 2003	Revised Visual Retention Test (VRT)	Visual-spatial perception	$P < .05$;
Schmidt 2004	MMSE;	Global cognitive function;	*P*=.16;
	Three word-recall lists (12 words each);	Memory;	*P*=.08;
	Stroop test;	Speed;	*P*=.002;
	Letter Digit Substitution test;	Hand	*P*=.25
	Perdue Peg Board test		
Elkins 2006	Modified MMSE;	Global cognitive function;	*P*=.001;
	Digit−Symbol Substitution test	Attention and psychomotor speed	*P*=.81
Li 2006	MMSE;	Global cognitive function;	$P < .05$;
	Block Test (BT);	Executive function;	$P < .01$;
	Clock-drawing Test (CDT);	Executive function;	$P < .01$;
Wang 2008	MMSE;	Global cognitive function; Direction memory;	$P > .05$;
	Clinical memory scale	Associated study,;	$P < .05$;
		Pictures freely memory;	$P > .05$;
		Meaningless figures recollection;	$P > .05$;
		Associational memory of portraits	$P > .05$;
		characteristic;	$P < .05$;
		Memory quotient	$P < .05$
Debette 2010	Neuropsychological tests	Verbal memory;	*NA*
		Visuospatial memory;	
		Paired-associate learning;	
		Executive function;	
		Non-memory	
Zhang 2010	MMSE;	Global cognitive function;	$P < .01$;
	CDT	Executive function;	$P < .01$;
Blum 2012	Neuropsychological tests	Memory;	$P < .001$;
		Language;	$P < .001$;
		Executive functioning/processing speed;	$P < .001$;
		Visuospatial ability	$P < .001$
Wen 2012	Montreal Cognitive Assessment Scale (MOCA)	Global cognitive function	$P < .01$
Wang 2012	MOCA	Global cognitive function	$P < .01$
Yuan 2012	MOCA	Global cognitive function	$P < .05$
Zhang 2012	MMSE;	Global cognitive function;	$P > .05$;
	MOCA	Global cognitive function	$P < .05$
Fang 2013	MMSE;	Global cognitive function;	$P = .002$;
	MOCA;	Global cognitive function;	$P < .001$;
	CDT;	Executive function;	$P = .027$;
	Verbal Fluency Test (BFT)	Executive function;	$P = .032$
Thong 2013	Neuropsychological tests	Attention;	$P < .05$;
		Language;	$P < .05$;
		Visuomotor speed;	$P < .05$;
		Visuo-construction;	$P < .05$;
		Executive function;	$P < .05$;
		Verbal memory;	$P < .05$;
		Visual memory	$P < .05$

Table 3 (*Continued*)

Study	Psychological tasks or test batteries	Nature of deficits	*P* value
Gao 2013	MOCA	Global cognitive function	$P < .01$
Qu 2013	MMSE	Global cognitive function	$P < .05$
Chen 2015	MMSE;	Global cognitive function;	$P = .004$;
	Neuropsychological tests	Memory;	$P < .05$;
		Attention;	$P > .05$;
		Visuospatial processing;	$P > .05$;
		Executive function;	$P < .05$;
		Language ability	$P < .05$;
Yang 2015	MOCA	Global cognitive function	$P < .01$

Discussion

The cerebral small vessel diseases, such as silent lacunar infarcts, leukoaraiosis, microbleeds, and cerebral atrophy, occurred more frequently in the elderly and were linked with cognitive decline.[28] A clinical study reported that more than half of patients with a first-ever lacunar stroke and without cognitive impairment showed minor neuropsychological alterations. These minor disturbances were mainly related to the presence of clinically silent lacunar infarcts, without any relationship to cognitive impairment with leukoaraiosis at this early stage of cerebral small vessel disease.[29] Our systematic review sought to generate definitive evidence about whether SBI could lead to cognitive dysfunction. The evidence from these studies suggested that SBI could be associated with cognitive dysfunction.

The results of this review indicated the large heterogeneity of SBI and cognitive function and emphasized 3major sources of heterogeneity. Firstly, the different neuropsychological tests used to cognitive function. Most of the included studies assessed using the MMSE and MOCA; these instruments were for global cognitive function, not specific or sensitive enough to draw conclusions about specific cognitive domains. Some studies relied on various neuropsychological tests to examine cognitive domains individually, and it was difficult to compare these results with the aggregate scores, using scales with different sensitivity and specificity, which was likely to cause heterogeneity in scoring. Secondly, Our study showed that different studies identified SBI lesions using different MRI protocols and diagnostic criteria, which might lead to heterogeneity in the numbers of MBs lesions detected and thus present major limitations for interpretation. Wardlaw et al developed definitions and imaging standards for cerebral small vessel disease. SBI was defined as a round or ovoid, subcortical, fluid-filled cavity (signal similar to CSF) of between 3 mm and about 15 mm in diameter, consistent with a previous acute small subcortical infarct or hemorrhage in the territory of 1 perforating arteriole. In the future, efforts are needed to adopt same criteria of SBI, which can discrepancies of SBI. Thirdly, different participants were included, such as healthy volunteers, stroke-free subject, and community-based subject, et al.

Our systematic review was consistent with findings from several studies that we excluded because they failed to satisfy the inclusion criteria. Northern Manhattan Study which was the population-based cohort study including 3,298 stroke-free participants indicated that SBI was associated with the global effect of worse cognitive performance adjusting conventional vascular risk factors. Moreover, this study further showed that location of SBI also was important; deep gray matter lesions were associated with impaired performance, whereas frontal infarcts were related to less cognitive flexibility.[30] A Japan study based on community-dwelling elderly volunteers aged more than 60 years also showed that SBI in apparently healthy elderly individuals seemed to form a distinctive group of people with vascular cognitive impairment without dementia.[31] The Osaki-Tajiri Project suggested that SCI might result in deteriorated attention regardless of global cognitive function, by interrupting the central cholinergic pathway.[32] These studies not only showed that SBI might be related with global cognitive dysfunction, but also indicated the different location of SBI might be associated with special domain of cognitive function.

Our systematic review has several limitations. Firstly, the included studies involved a relatively small number of participants and the heterogeneity of their subjects and poor methods. Prospective lager cohort studies are needed to confirm the association between SBI and cognitive function. Secondly, most included studies used the MMSE and MOCA scales to assess global cognitive function. Unfortunately, the MMSE and MOCA are low-resolution screening instruments that do not permit detailed analysis of specific domains of cognitive function. Some studies in our systematic review relied on neuropsychological tests and neurocognitive tests to examine cognitive domains

Table 4. *Results of risk of bias questions to assess the quality of included studies*

Type of bias	Selection			Detection		Misclassification	Reporting		Confounding
Question	Was the study sample randomly selected or a community-dwelling population to minimize the risk of selection bias?	Were the inclusion and exclusion criteria adequately described?	Was the study's primary objective to assess whether SBI is predictive of all cognitive function or any domain of cognitive function?	Were the investigators blinded to the clinical history of patients during ascertainment of SBI?	Did more than one investigator assess for the presence of SBI?	Did the investigators describe a method by which SBI was differentiated from dilated perivascular spaces?	Were the investigators blinded to the clinical history of patients during ascert-ainment of neuropsy-chological battery?	Did more than one investigator assess for the presence of neuropsycho-logical battery?	Were data adjusted for covariate risk factors to minimize the risk of confounding bias?
Answer	Yes (+) or no (-)	Yes (+) or no (-)	Yes (+) or no (-)	Yes (+) or no (-)	Yes (+) or no (-)	Yes (+) or no (-)	Yes (+) or no (-)	Yes (+) or no (-)	Yes (+) or no (-)
Price 1997	+	+	+	-	-	+	-	+	+
Maeshima 2002	-	+	+	+	+	+	-	-	+
Li 2003	-	+	+	-	-	-	-	-	+
Vermeer 2003	+	+	+	+	-	+	-	-	+
Zhong 2003	-	+	+	-	-	-	-	-	+
Schmidt 2004	+	+	+	-	-	+	-	-	+
Elkins 2006	+	+	+	+	+	-	-	-	+
Li 2006	-	+	+	-	-	-	-	-	+
Wang 2008	-	+	+	-	-	-	-	-	+
Debette 2010	+	+	+	-	-	+	-	-	+
Zhang 2010	-	+	+	-	-	-	-	-	+
Blum 2012	+	+	+	+	+	+	-	-	+
Wen 2012	-	+	+	-	-	-	-	-	+
Wang 2012	-	+	+	-	-	-	-	-	+
Yuan 2012	-	+	+	-	-	-	-	-	+
Zhang 2012	-	+	+	-	-	-	-	-	+
Fang 2013	-	+	+	+	+	+	-	-	+
Thong 2013	+	+	+	-	-	+	-	-	+
Gao 2013	-	+	+	-	-	-	-	-	+
Qu 2013	-	+	+	-	-	-	-	-	+
Chen 2015	-	+	+	-	+	+	-	+	+
Yang 2015	+	+	+	-	-	+	-	+	+

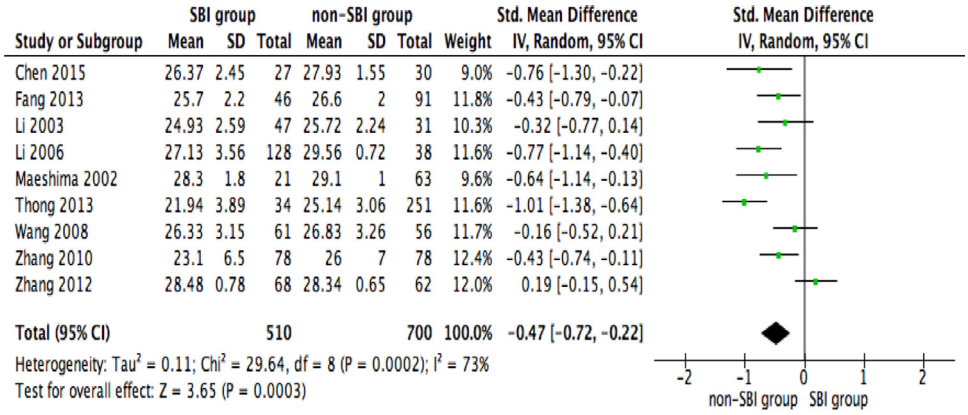

Figure 2. *Meta-analysis of continuous data on the relationship between SBI and Mini-Mental State Examination.*

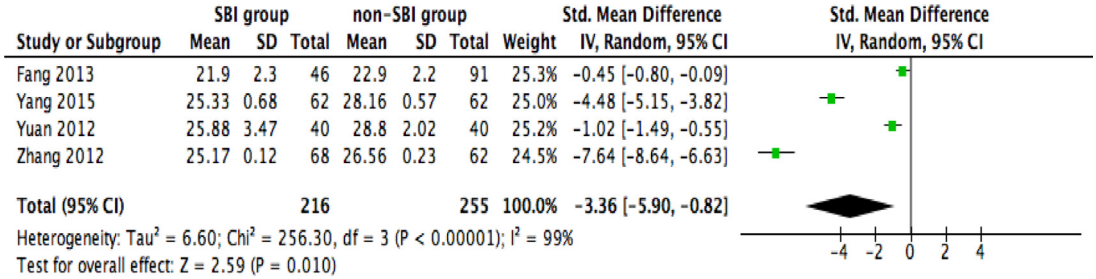

Figure 3. *Meta-analysis of continuous data on the relationship between SBI and Montreal Cognitive Assessment Scale.*

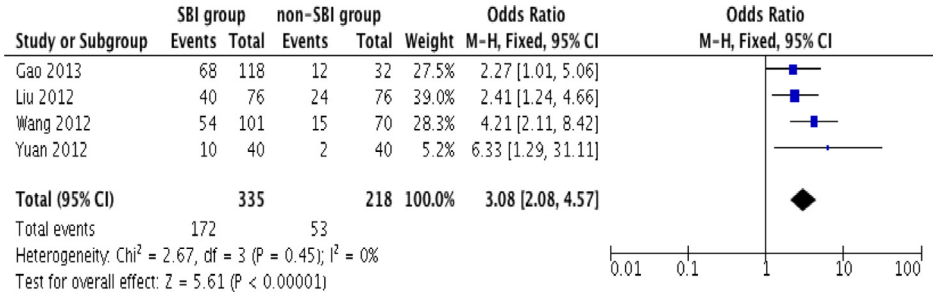

Figure 4. *Meta-analysis of dichotomous data on the relationship between SBI and Montreal Cognitive Assessment Scale.*

individually, but it was difficult to compare these results with the aggregate scores. In the future, diverse neuropsychological instrument could be analyzed for pooled reviews e.g. z scores**.** Thirdly, our systemic review had generally of poor methodological quality. Only 31.57% studies were deemed to be of high quality; some studies did not involve blinded assessment of SBI and cognitive function, which lead to relative poor quality. In the further study, we should use well-designed longitudinal studies combining standard neuroimaging and neuropsychological tests, while we should as much as possible adopt blinded assessment of SBI lesions and neuropsychological tests, which can decrease the measurement bias. Fourthly, for some reason, some necessary information was not provided in the original article, which led to our systematic review loss of some important information and affected the quality of our study.

Based on available evidence, we suggest that "silent" brain infarcts were not entirely asymptomatic because it seems to be associated with cognitive dysfunction. To examine this association as rigorously as possible, well-designed longitudinal studies combining neuroimaging and standard neuropsychological testing are needed in order to improve early diagnosis and treatment SBI.

Table 5. *The characteristics of SBI*

Study	Number	Size (mm)	Shape	Location	Signal characteristics			Was hypointense rim on T2*-weighted imaging**	Was distinguished from perivascular spaces**
					T1	T2	FLAIR		
Price 1997	NA	NA	NA	Cortex, subcortex	Hypointense	Hyperintense	NA	NA	Yes
Maeshima 2002	One or many	>5mm	NA	NA	NA	Hyperintense	NA	NA	NA
Li 2003	NA	NA	NA	Cortex	Hypointense	Hyperintense	NA	NA	NA
Vermeer 2003	NA	>3 mm	Focal areas	NA	Hypointense	Hyperintense	NA	NA	Yes
Zhong 2003	One or many	NA	NA	Cortex, subcortex	NA	NA	NA	NA	NA
Schmidt 2004	NA	>2 mm	NA	Cortex, subcortex	Hypointense	Hyperintense	NA	NA	NA
Elkins 2006	NA	>3 mm	NA	Cortex, subcortex	Hypointense	Hyperintense	NA	NA	NA
Li 2006	One or many	NA	NA	NA	NA	NA	NA	NA	NA
Wang 2008	One or many	>15 mm	NA	Cortex, subcortex	NA	NA	NA	NA	NA
Debette 2010	NA	>3 mm	NA	Subcortex	CSF intensity	CSF intensity	NA	NA	Yes
Zhang 2010	One or many	NA	NA	NA	NA	NA	NA	NA	NA
Blum 2012	One or many	3-15 mm	Ovoid lesion	Cortex, subcortex	CSF intensity	CSF intensity	NA	NA	Yes
Wen 2012	NA	NA	NA	NA	NA	NA	NA	NA	NA
Wang 2012	One or many	NA	NA	Cortex, subcortex	NA	NA	NA	NA	NA
Yuan 2012	One or many	5-20 mm	NA	Cortex, subcortex	NA	NA	NA	NA	NA
Zhang 2012	One or many	NA	NA	NA	NA	NA	NA	NA	NA
Fang 2013	NA	3-15 mm	Focal cavitated lesion	Subcortex	Hypointense	Hyperintense	NA	NA	NA
Thong 2013	NA	3-15 mm	Spotty areas	Subcortex	CSF intensity	CSF intensity	CSF intensity	Yes	Yes
Gao 2013	NA	NA	NA	Cortex, subcortex	NA	NA	NA	NA	NA
Qu 2013	One or many	NA	NA	NA	NA	NA	NA	NA	NA
Chen 2015	NA	3-15 mm	Round, ovoid lesion	Subcortex	Decreased attenuation similar to cerebrospinal fluid−filled cavities	Increased signal relative to white matter	Increased signal relative to white matter		NA
Yang 2015	NA	>3 mm	Spotty areas	Cortex, subcortex	Hypointense	Hyperintense	Hyperintense	NA	NA

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Potential Conflicts of Interest

None of the authors had any conflict of interest with any pharmaceutical companies or organizations in carrying out this study.

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