# Association between Homocysteine and Cerebral Small Vessel Disease: A Meta-Analysis

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*Background:* This study aimed to evaluate whether elevated homocysteine levels is associated with risk of different subtypes of cerebral small vessel disease (CSVD) by using meta-analysis. *Materials and Methods:* Electronic databases were systematically searched up to April 2018 for collecting the studies reporting homocysteine levels in CSVD or CSVD subtypes. After an inclusion and exclusion criteria, the data was extracted. All data was analyzed using Stata software v.12.0 (Stata Corp LP, College Station, TX). The standardized mean difference (SMD) and 95% confidence interval (CI) were used to compare continuous variables. *Results:* Eighteen studies met eligibility criteria with 5088 participants (1987 patients with CSVD and 3101 controls) included in the meta-analysis. Meta-analysis revealed that, compared with the controls group, the CSVD group had significantly higher homocysteine levels, with the SMD of .50 and 95% CI (.36-.64). Subgroup analyses suggested white matter lesion had significantly higher levels of homocysteine compared with controls (SMD = .56, 95% CI .39-.73), followed by silent brain infarction (SMD = .33, 95% CI .24-.42) and lacunar infarction (SMD = .17, 95% CI −.06 to .40). *Conclusions:* This meta-analysis found that CSVD or CSVD subtypes have a significantly higher homocysteine levels than in controls. Further prospective population-based studies are needed to longitudinally evaluate the association between homocysteine levels and progression of different CSVD subtypes. **Key Words:** Cerebral small vessel disease—stroke—homocysteine—meta-analysis.


## Introduction

Cerebral small vessel disease (CSVD) refers to a series of pathological processes affecting the small arteries, arterioles, venules, and capillaries of the brain.[1] Now, CSVD is frequently used to describe a syndrome of clinical, pathological, and neuroimaging findings, which are thought to associate with stroke and vascular dementia.[2] According to the results of previous studies, CSVD contributes to 20% of ischemic stroke and 45% of dementias, and causes the huge cost to our society.[3-5] The inter-related imaging features on the brain parenchyma of CSVD, is visible by using sophisticated brain-imaging techniques, include white matter lesion (WML), lacunar infarction (LI), cerebral microbleed (CMB), enlarged perivascular space (EPVS), and brain atrophy.[2] Moreover, silent brain

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Received April 12, 2018; accepted April 26, 2018.

Authors' contributions: Xiangyu Piao, Guangyao Wu, Jianlin Wu, and Qiumin Qu designed the study, analyzed and interpreted the results, and drafted the manuscript. Pei Yang, Jing Shen, and Ailing De acquired the data. All authors participated in analysis and interpretation the results. All approved the final version of the manuscript for submission.

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1052-3057/$ - see front matter



https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.04.035

infarction (SBI), defined as a cerebral ischemic evident by brain imaging, but lacks a clinical syndrome, and is thought to be a marker of CSVD.[6]

The relationships with CSVD are still incompletely understood. Age, gender, hypertension, diabetes mellitus, hypercholesterolemia, and smoking are the traditional risk factors of CSVD.[7] Homocysteine as a naturally occurring amino acid, nevertheless, is closely related with endothelial dysfunction and extracellular matrix proliferation that seems able to cause vessel damage.[8] For the past decade, many studies have suggested that elevated homocysteine levels are a risk factor for a number of occlusive vascular diseases.[9] In addition, recent studies have indicated that high homocysteine levels are also associated with CSVD.[10] However, as mentioned earlier, the literature regarding the correlation between homocysteine and specific CSVD subtypes is inconsistent. This discrepancy in these studies is attributable to the relatively small sample sizes, study design, and subjects' heterogeneity. Therefore, a meta-analysis was performed to derive a more precise estimation and critically evaluate the homocysteine levels in patients with CSVD for overcoming the limitations of individual studies and decrease inconsistencies. Furthermore, a subgroup of the homocysteine levels in different CSVD subtypes was performed.

## Materials and Methods

### *Literature Search and Selection Criteria*

This study was conformed to a protocol of the Meta-analysis of Observational Studies in Epidemiology guidelines.[11] Two reviewers screened the databases including PubMed, EMBASE, and the Cochrane Library between January 1990 and April 2018, using specific search strategies: ((“white matter” OR leukomalacia OR leukoaraiosis) OR (infarct* OR infarction* OR lacune*) OR (microbleed* OR microhemorrhag* OR microhaemorrhag*) OR (Virchow-Robin or “perivascular space*”) OR (atrophy OR volume*) OR (“cerebral small vessel disease*” OR “small vessel disease*”)) AND (tHcy OR Hcy OR homocysteine OR hyperhomocysteimia OR hyperhomocysteinemia OR HHcy). Reference lists of eligible studies and relevant reviews were additionally searched by hands.

Studies that met the following criteria: (1) case-control or cross-sectional studies in humans, (2) published in English with peer review, (3) cerebral lesions were caused by CSVD or accorded with the imaging performance of CSVD, and (4) reported the homocysteine results using mean and standard deviation were eligible. We excluded the following studies: (1) case reports, and case series; (2) animal experiments; (3) non-English; (4) large vessel diseases or other causes of stroke; (5) had no clear homocysteine results; and (6) special research diseases, such as multiple sclerosis, diabetes, rheumatoid arthritis, severe functional disorders of the kidney, liver, heart, and lung, etc. In cases of multiple publications from the overlapping cohorts, only the most recent comprehensive results with the largest sample size were selected. If there was any disagreement between reviewers, a team consensus was reached based on the predefined selection criteria.

### *Data Extraction and Study Quality Assessment*

The following data from each included study were extracted: first author's name, year of publication, country of origin, sample characteristics (population size, age, sex, hypertension, diabetes, smoking, and alcohol), homocysteine levels (mean ± standard deviation), and CSVD subtypes. The assessment of study quality was based on guidelines developed by the Newcastle–Ottawa Scale and modified according to a previous study.[12]

### *Statistical Analysis*

All meta-analysis were performed using Stata 12.0 (Stata Corp LP, College Station, TX). Standardized mean difference (SMD) with 95% confidence interval (CI) was used for continuous values. Heterogeneity among studies was measured by the $I^2$ tests, and studies with $I^2$ higher than 50% were considered to have high heterogeneity.[13] A fixed effects model was used when there was no significant heterogeneity among studies; otherwise, a random effects model was used. To identify the possible source of heterogeneity within the included studies, subgroup analyses were performed based on subtypes of CSVD. Funnel plots were used to evaluate potential systematic bias in studies. Two-sided *P* values less than .05 were considered as a statistical significance.

## Results

### *Study Characteristics and Quality*

The initial search identified 424 possible studies after screening abstracts, and 26 studies were considered eligible after a detailed review, but 8 were excluded because of overlapping, resulting in 18 studies,[14-31] involving 5088 participants (1987 patients with CSVD and 3101 controls), for inclusion in this meta-analysis (Fig 1). Of the included studies, 6 reported SBI type,[14-19] 8 reported WML type,[20-26] 2 reported LI type,[27,28] 1 reported CMB type,[21] and 3 have no specific CSVD subtypes.[29-31] No eligible study reported EPVS or brain atrophy. The characteristics of these 18 studies and scores of study quality based on guidelines developed by the Newcastle–Ottawa Scale were shown in Table 1. The studies included in the meta-analysis were generally of moderate-to-high quality.