# Chinese Herbal Medicine for Patients with Vascular Cognitive Impairment No Dementia: Protocol for A Systematic Review

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| **Keywords:** | Chinese herbal medicine, Vascular cognitive impairment no dementia, Protocol, Systematic review |
Chinese Herbal Medicine for Patients with Vascular Cognitive Impairment No Dementia: Protocol for A Systematic Review

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ABSTRACT

Introduction: The aim of this systematic review is to assess the efficacy and safety of Chinese herbal medicine (CHM) for the treatment of patients with vascular cognitive impairment but no dementia.

Methods and analysis: We will perform a comprehensive retrieval using the following electronic databases: PubMed, Cochrane Library, EMBASE, CINAHL, Chinese Biomedical Literature Service System (SinoMed), China National Knowledge Infrastructure (CNKI), Chinese Scientific Journals Database (VIP), Wan-fang database and other sources. After screening the studies, the quality of all included trials will be assessed according to the Cochrane Collaboration’s risk of bias tool. A meta-analysis of randomized controlled trials (RCTs) will be conducted by using RevMan 5.3 software. Funnel plot analysis and Egger’s test will be used to assess publication bias, if possible. The quality of evidence will be assessed by the GRADE system.
Dissemination: This systematic review will be disseminated in a peer-reviewed journal and a relevant conference presentation.

Trial registration number: PROSPERO CRD 42015023682

Strengths and limitations of this study

- This systematic review will conduct a comprehensive, objective and normative systematic review on the efficacy and safety of Chinese herbal medicine for vascular cognitive impairment in participants without dementia.
- Study screening, data extraction and assessment of the risk of bias will be conducted independently by two researchers.
- Currently, there is a lack of internationally recognized diagnostic criteria in vascular cognitive impairment without dementia. Therefore subgroup analyses will be carried out to explore any sources of heterogeneity.

INTRODUCTION

As the population ages and there is improved survival from vascular diseases, and cerebrovascular disease (CVD) has become a more important cause of cognitive dysfunction and dementia. Recently, the term “vascular cognitive impairment (VCI)” has been introduced to describe the entire spectrum of cognitive dysfunction—ranging from cognitive impairment without dementia to dementia—attributable to all forms of cerebrovascular disease.1 2 There are three subtypes of VCI: vascular cognitive impairment no dementia (VCIND), vascular dementia (VaD) and mixed VaD and Alzheimer’s Disease (AD).3 Among them, VCIND is characterized by early or mild cognitive impairment (MCI) due to cerebrovascular injuries with an insidious nature.4 It may be considered to be the prodromal stage of VaD,5 with occurrence in 26.9% of patients approximately 3 months after stroke onset.6 A cohort study which included 149 participants with VCIND showed that 46% cases were observed to develop dementia, and 52% of these cases died within 5 years.7 Another community-based, cross-sectional study in China also reported the overall prevalence of post-stroke cognitive impairment (PSCI) was 80.97% (95%CI: 77.82%-84.11%), while that of
non-dementia PSCI (PSCI-ND) and post-stroke vascular dementia (PSD) were 48.91% (95%CI: 44.91%-52.92%) and 32.05% (95%CI: 8.32%-35.79%) respectively.\(^8\)

Fortunately, VCIND is a potentially treatable and preventable cause of dementia in later life\(^9\) and early diagnosis and appropriate interventions may contribute to the improvement of the prognosis.\(^10\) But there are limited treatment options to improve cognition and function in VCI.\(^1\) Chinese herbal medicine, which has been used for thousands of years in China, has been considered effective for improving cognitive function.\(^11\) A meta-analysis showed that CHM appears to be safer and more effective than placebo or Western medicine in the treatment of vascular dementia.\(^12\) Another meta-analysis which focused on the efficacy and safety of CHM for VCIND,\(^13\) but this review was limited to Chinese medical databases, search terms were limited, and there was no PRISMA flow chart. Therefore, we carry out a more comprehensive and normative systematic review to provide objective and scientific evidence on CHM for the treatment of VCIND.

METHODS AND ANALYSIS

Inclusion and exclusion criteria for study selection

Types of studies

Randomized controlled trials (RCTs) that used CHM or a combination of CHM and routine pharmacotherapy as treatment measures will be eligible for inclusion. Language will be limited to English and Chinese. Trials without a control group will be excluded.

Types of participants

1. No internationally recognized diagnostic criteria currently exist and no laboratory tests are available for VCIND diagnosis.\(^14\)\(^15\) Therefore this study will include patients who were diagnosed with VCIND based on diagnostic criteria used in international clinical trials \(^4\)\(^16\)\(^17\) or Chinese expert consensus.\(^18\)\(^19\)\(^20\)

2. The study will include all types of patients regardless of their age, sex, ethnicity, education or economic status and whether or not they were outpatients or inpatients.

3. Patients should not meet the diagnostic criteria for any type of dementia.

Types of Interventions
Studies reporting any type of CHM treatment will be included. The CHM could be used alone or combined with routine pharmacotherapy. We will exclude the trials if a different routine pharmacotherapy is used in the treatment group to that used in the control group. Trials in which the interventions are CHM in combination other Chinese medicine therapies (e.g. acupuncture, moxibustion, massage, tai chi, et al) will be excluded.

**Types of Comparators**

Comparison interventions, including placebo control, no treatment, routine pharmacotherapy, routine care and other conventional treatments, will be included.

**Primary outcome assessments**

Primary outcome measures for assessment should include at least one of the internationally recognized evaluation scales, which refer to one of the following aspects: cognitive function, activities of daily living, behavioral and psychological symptoms of dementia (BPSD) or global evaluation scales (Table 1).

**Secondary outcome assessments**

The secondary outcome assessments will be study dropouts, the incidence and severity of adverse effects.

**Search methods for identification of studies**

**Electronic searches**

We will perform a comprehensive retrieval for studies that evaluated the efficacy and safety of CHM in patients with VCIND in major Chinese and English medical databases. The literature search will be performed using the English medical databases: PubMed, Cochrane Library, EMBASE, CINAHL from their respective inceptions to July 2015. The Chinese language databases will include: Chinese Biomedical Literature Service System (SinoMed) from 1978 to July 2015, China National Knowledge Infrastructure (CNKI) from 1979 to July 2015, Chinese Scientific Journals Database (VIP) from 1989 to July 2015, and Wan-fang database from 1998 to July 2015. The following subject terms and key words will be used in the search: (‘vascular cognitive impairment’ OR ‘mild cognitive impairment’ OR...
post-stroke cognitive impairment’ OR ‘VCI’) and ( ‘Medicine, Chinese Traditional’ OR ‘Drugs, Chinese Herbal’ OR ‘herbal medicine’ OR ‘Chinese traditional medicine’ OR ‘Traditional Chinese medicine’ ). Chinese translations of these search terms will be utilized to search the Chinese databases. The search strategy for PubMed is given in Table 2.

Other sources
Studies from other sources will also be obtained from the following sources:
1) Google Scholar (http://scholar.google.com) and Baidu Scholar (http://xueshu.baidu.com/);
2) Clinical Trials.gov (http://www.clinicaltrials.gov) and Chinese Clinical Trial Registry (http://www.chictr.org.cn/);
3) The reference lists of the retrieved articles.

Data extraction and quality evaluation
EndNote X6 software will be used to manage the data extraction and the process of removing duplications. A data extraction EXCEL table will be designed which includes the characteristics of studies, randomization, blinding, interventions, comparators, outcomes, study dropouts, the incidence and details of adverse effects.
Two researchers (M Feng and JM Lu) will extract and double-check the data from the included articles. Any discrepant data will be reviewed by discussion with another team member (SN Liu). The details of the study selection will be shown in a PRISMA flow chart (Figure 1).

Risk of bias assessment of included studies
The quality of all included trials will be assessed by ‘risk of bias assessment tool’ according to the Cochrane Handbook 5.1. Two researchers (M Feng and JM Lu) will assess the quality of the included studies independently. Any different views will be discussed with another team member (SN Liu). The risk of bias in included studies will be evaluated according to the eight domains: randomization sequence generation, randomization allocation concealment, blinding of participants, blinding of personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias.
Strategy for data synthesis and statistical analysis

We will use RevMan 5.3 software for data analysis. For continuous data collected using the same measurement scale, we will calculate weighted mean difference (WMD) and 95% confidence intervals (CIs). For continuous data collected using similar measurement scales for the same outcome, we will calculate standardized mean differences (SMD) with 95% CIs. For dichotomous outcomes, we will use risk ratio (RR) with 95% CI and p values to assess the efficacy and safety of CHM. A standard chi-squared statistic and $I^2$ statistic will be used to test heterogeneity between groups. Data will be analyzed with a fixed-effect model if no statistical heterogeneity was observed between subgroups ($P \geq 0.1, I^2 \leq 50\%$). In the presence of heterogeneity ($P < 0.1, I^2 > 50\%$), a random-effect model will be used and the possible causes of heterogeneity will be examined.

Dealing with missing data or unclear scale type

We will attempt to contact the authors of included studies in which there is missing data or unclear source of the evaluation scales through e-mail or telephone. For missing data, if we fail to obtain sufficient data after contacting authors, an intention-to-treat analysis will be performed if feasible.

Planned subgroup analyses

Where possible we will perform subgroup analyses based on intervention type (CHM or CHM in combination with routine pharmacotherapy), different control measures, different durations and different diagnostic criteria.

Sensitivity analysis

Where feasible, we will carry out sensitivity analyses to verify the robustness of the study conclusions and investigate any sources of heterogeneity. These may be according to the methodological quality evaluation, severity of included patients, ingredients of the CHMs or other parameters.

Assessment of reporting biases

We will use funnel plots to detect potential reporting biases if more than 10 studies are included in the meta-analysis. The Egger's test will be used to assess if the funnel
plots are symmetric using Stata 11.0 software.

**Assessment of Quality of Evidence**

The Cochrane Collaboration Network GRADE (The Grading of Recommendations Assessment Development and Evaluation) will be used to assess the results in this systematic review. We will create a Summary of Finding (SoF) table in http://www.guidelinedevelopment.org/.

**Ethics and dissemination**

Ethical approval will not be required for this systematic review because there are no concerns regarding patient’s privacy. The results will be disseminated in a peer-reviewed journal and presented at a relevant conference.

**DISCUSSION**

VCIND belongs to *Jianwang, Shanwang, Daibing* in Chinese traditional medicine. CHMs have been cited for treating memory disorders in the classical herbal literature for many centuries and the results of pre-clinical and clinical studies suggest that CHM could improve cognitive decline. A good systematic review can integrate valid clinical information and provide a basis for rational decision making, but systematic reviews require a thorough, objective and reproducible search of a range of sources to identify as many relevant studies as possible and help to minimize bias, such as publication bias and language bias. This systematic review will provide a comprehensive and objective assessment of the efficacy and safety of CHM for VCIND, in order to assist clinicians and patients to select the most appropriate treatment options.

**Contributors**

Chuanjian Lu, Charlie Changli Xue, Xinfeng Guo and Anthony Lin Zhang conceived and designed the study. The manuscript of this protocol was drafted by Mei Feng, Jingmin Lu and Brian H. May and revised by Chuanjian Lu and Charlie Changli Xue. Mei Feng, Jingmin Lu designed search strategies and will perform the search, screening and assessment of the risk of bias independently. Mei Feng and Brian H. May will analyse and interpret the data. Shaonan Liu will arbitrate any disagreements.
during the review. All authors approved the final version of this protocol.

Competing interests: None.

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REFERENCES


Table 1  Summary of primary outcome assessments

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<th>Outcome measures</th>
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<tr>
<td>Cognitive Function</td>
<td>• MMSE (Mini Mental Status Examination)</td>
</tr>
<tr>
<td></td>
<td>• HDS (Hasagawa Dementia Scale)</td>
</tr>
<tr>
<td></td>
<td>• ADAS-cog (Alzheimer’s disease assessment scale-cognitive)</td>
</tr>
<tr>
<td></td>
<td>• MoCA (Montreal Cognitive Assessment)</td>
</tr>
<tr>
<td></td>
<td>• WMS (Wechsler Memory Scale)</td>
</tr>
<tr>
<td>Activities of Daily Living</td>
<td>• Activities of Daily Living</td>
</tr>
<tr>
<td></td>
<td>• ADCS-ADL (Alzheimer disease cooperative study-ADL inventory)</td>
</tr>
<tr>
<td></td>
<td>• FAQ (Functional activity questionnaire)</td>
</tr>
<tr>
<td>Behavioral and Psychological Symptoms of Dementia (BPSD)</td>
<td>• NPI (neuropsychiatric inventory)</td>
</tr>
<tr>
<td></td>
<td>• HAMD (Hamilton depression scale)</td>
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<tr>
<td></td>
<td>• CSDD (Cornell scale for depression in dementia)</td>
</tr>
<tr>
<td>Global Evaluation</td>
<td>• CDR (clinical dementia rating)</td>
</tr>
<tr>
<td></td>
<td>• CIBIC-plus (clinicians’ interview-based impression of change-plus)</td>
</tr>
<tr>
<td></td>
<td>• GDS (global deteriorate scale)</td>
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Table 2  Search strategy used in PubMed database

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<tr>
<td>1</td>
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<td>2</td>
<td>mild cognitive impairment</td>
</tr>
<tr>
<td>3</td>
<td>post-stroke cognitive impairment</td>
</tr>
<tr>
<td>4</td>
<td>VCI</td>
</tr>
<tr>
<td>5</td>
<td>1 or 2−4</td>
</tr>
<tr>
<td>6</td>
<td>Medicine, Chinese Traditional</td>
</tr>
<tr>
<td>7</td>
<td>Drugs, Chinese Herbal</td>
</tr>
<tr>
<td>8</td>
<td>herbal medicine</td>
</tr>
<tr>
<td>9</td>
<td>Chinese traditional medicine</td>
</tr>
<tr>
<td>10</td>
<td>Traditional Chinese medicine</td>
</tr>
<tr>
<td>11</td>
<td>6 or 7−10</td>
</tr>
<tr>
<td>12</td>
<td>5 and 11</td>
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Figure 1 Flow diagram of selection process

- Records identified through database searching (n = )
- Additional records identified through other sources (n = )
- Records after duplicates removed (n = )
- Records screened (n = )
- Full-text articles assessed for eligibility (n = )
- Full-text articles excluded, with reasons (n = )
- Studies included in qualitative synthesis (n = )
- Studies included in quantitative synthesis (meta-analysis) (n = )
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**Primary Subject Heading**: Neurology  
**Secondary Subject Heading**: Complementary medicine  
**Keywords**: Chinese herbal medicine, Vascular cognitive impairment no dementia, Protocol, Systematic review
Chinese Herbal Medicine for Patients with Vascular Cognitive Impairment No Dementia: Protocol for A Systematic Review

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ABSTRACT

Introduction: The aim of this systematic review is to assess the efficacy and safety of Chinese herbal medicine (CHM) for the treatment of patients with vascular cognitive impairment but no dementia.

Methods and analysis: We will perform a comprehensive retrieval in the following electronic databases: PubMed, Cochrane Library, EMBASE, CINAHL, Chinese Biomedical Literature Service System (SinoMed), China National Knowledge Infrastructure (CNKI), Chinese Scientific Journals Database (VIP), Wan-fang database and other sources. After screening the studies, the methodological quality of all included trials will be assessed according to the risk of bias instrument provided by the Cochrane Collaboration. A meta-analysis of randomized controlled trials (RCTs) will be conducted by using RevMan 5.3 software. Funnel plot analysis and Egger’s test will be used to assess publication bias, if possible. The quality of evidence will be assessed by the GRADE system.
Dissemination: This systematic review will be disseminated in a peer-reviewed journal and a relevant conference presentation.

Trial registration number: PROSPERO CRD 42015023682

Strengths and limitations of this study

- This study is a comprehensive, objective and normative systematic review on the efficacy and safety of Chinese herbal medicine for vascular cognitive impairment in participants without dementia.
- Study screening, data extraction and assessment of the risk of bias will be conducted independently by two researchers.
- Currently, there is a lack of internationally recognized diagnostic criteria in vascular cognitive impairment without dementia. Therefore subgroup analyses will be carried out to explore any sources of heterogeneity.

INTRODUCTION

As the population ages and survival from vascular disease is improved, cognitive dysfunction and dementia caused by cerebrovascular disease (CVD) have become prevalent. Recently, vascular cognitive impairment (VCI) has been introduced to describe the entire spectrum of cognitive dysfunction — ranging from cognitive impairment without dementia to dementia — attributable to all forms of cerebrovascular disease. There are three subtypes of VCI: vascular cognitive impairment no dementia (VCIND), vascular dementia (VaD) and mixed VaD and Alzheimer’s Disease (AD). Among them, VCIND is characterized by early or mild cognitive impairment (MCI) due to cerebrovascular injuries with an insidious nature. It may be considered to be the prodromal stage of VaD, with occurrence in 26.9% of patients approximately 3 months after stroke onset. A cohort study which included 149 participants with VCIND showed that 46% cases were observed to develop dementia, and 52% of these cases died within 5 years. Another community-based, cross-sectional study in China also reported the overall prevalence of post-stroke cognitive impairment (PSCI) was 80.97% (95%CI: 77.82%-84.11%), while that of
non-dementia PSCI (PSCI-ND) and post-stroke vascular dementia (PSD) were 48.91% (95%CI: 44.91%-52.92%) and 32.05% (95%CI: 8.32%-35.79%) respectively.\(^8\)

Fortunately, VCIND is potentially treatable and preventable.\(^3\) Early diagnosis and appropriate interventions may contribute to the improvement of the prognosis.\(^9\) But there are limited treatment options to improve cognition and function in VCI.\(^1\) Chinese herbal medicine, which has been used for thousands of years in China, has been considered promising for improving cognitive function.\(^10\) A meta-analysis of CHM for VaD showed that there were significant benefits associated with CHM groups in terms of effective rate, Mini-Mental State Examination (MMSE) scores, Hasegawa Dementia Scale (HDS) scores at the end of treatment. Furthermore, fewer adverse events occurred in the treatment group. In light of this evidence, CHM appears to be safe and effective for VaD.\(^11\) A meta-analysis which focused on the efficacy and safety of CHM for VCIND indicated that CHM could improve patients’ cognitive and behavioral functions compared to the treatment with Western medicine.\(^12\) But the information source was limited to Chinese medical databases and there was no flow chart to show the study screening process. Therefore, we aim to carry out a more comprehensive and normative systematic review to provide objective and scientific evidence on CHM for the treatment of VCIND.

**METHODS AND ANALYSIS**

**Inclusion and exclusion criteria for study selection**

**Types of studies**

Randomized controlled trials (RCTs) which used CHM or a combination of CHM and routine pharmacotherapy as treatment measures will be eligible. Language will be limited to English and Chinese.

**Types of participants**

1. No internationally recognized diagnostic criteria currently exist and no laboratory tests are available for VCIND diagnosis.\(^13\)\(^14\) Therefore this study will include patients who were diagnosed with VCIND based on diagnostic criteria used in international clinical trials\(^15\)\(^16\)\(^17\) or Chinese expert consensus.\(^18\)\(^19\)\(^20\)

2. The study will include all types of patients regardless of their age, sex, ethnicity,
education or economic status and whether or not they were outpatients or inpatients.

3. Patients should have acquired cognitive impairment, but not meet the diagnostic
criteria for any type of dementia. Furthermore, their cognitive impairment was judged
to have vascular risk factors or cerebrovascular disease (including clinical features or
radiographic features).

**Types of Interventions**

Studies reporting any type of CHM treatment will be included. The CHM could be
used alone or combined with routine pharmacotherapy. Studies where the control
group is different from the pharmacotherapy in the intervention group will be
excluded. Trials in which the intervention group include any other Chinese medicine
therapies (e.g. acupuncture, moxibustion, massage, *taichi*, et al) will be excluded.

**Types of Comparators**

Comparators will include placebo control, no treatment, routine pharmacotherapy,
routine care and other conventional treatments.

**Primary outcome assessments**

Primary outcome measures for assessment should include at least one of the
internationally recognized evaluation scales, which refer to one of the following
aspects: cognitive function, activities of daily living, behavioral and psychological
symptoms of dementia (BPSD) or global evaluation scales (Table 1).

**Secondary outcome assessments**

The secondary outcome assessments will be the incidence and severity of adverse
events.

**Search methods for identification of studies**

**Electronic searches**

We will perform a comprehensive retrieval for studies that evaluate the efficacy and
safety of CHM in patients with VCIND in major Chinese and English medical
databases including PubMed, Cochrane Library, EMBASE, CINAHL, Chinese
Biomedical Literature Service System (SinoMed), China National Knowledge
Infrastructure (CNKI), Chinese Scientific Journals Database (VIP) and Wan-fang
database from their respective inceptions to July 2015. The following subject terms
and key words will be used in the search: (‘vascular cognitive impairment’ OR ‘mild cognitive impairment’ OR ‘post-stroke cognitive impairment’ OR ‘VCI’) and (‘Medicine, Chinese Traditional’ OR ‘Drugs, Chinese Herbal’ OR ‘herbal medicine’ OR ‘Chinese traditional medicine’ OR ‘Traditional Chinese medicine’). Chinese translations of these search terms will be utilized to search the Chinese databases. The search strategy for PubMed is given in Table 2 and detailed steps are shown in Appendix 1.

**Other sources**

Studies from other sources will also be obtained from the following sources:

1. Google scholar (http://scholar.google.com) and Baidu scholar (http://xueshu.baidu.com/);
2. Clinical Trials.gov (http://www.clinicaltrials.gov) and Chinese Clinical Trial Registry (http://www.chictr.org.cn/);
3. The reference lists of the retrieved articles.

**Data extraction and quality evaluation**

EndNote X6 software will be used to manage the literature and the process of removing duplications. A data extraction EXCEL table will be designed which includes the data on age, sex, duration, education level, life style (e.g. smoking, alcohol consumption), vascular risk factors (e.g. hypertension, hyperlipidemia, diabetes), medical comorbidities, concurrent medications (e.g. anti-platelet aggregation drugs, anti-hypertensive drugs, hypoglycemic drugs), randomization, blinding, interventions, comparators, outcomes, study dropouts, the incidence and details of adverse effects. Two researchers (M Feng and JM Lu) will extract and double-check the data from the included articles. Any discrepant data will be reviewed by discussion with another team member (SN Liu). The details of the study selection will be shown in a PRISMA flow chart (Figure 1).

**Risk of bias (ROB) assessment of included studies**

The methodological quality of all included trials will be assessed by ‘risk of bias assessment tool’ according to the Cochrane Handbook 5.1 by two independent researchers (M Feng and JM Lu). Any different views will be discussed with another.
team member (SN Liu). The risk of bias in included studies will be evaluated according to the eight domains: randomization sequence generation, randomization allocation concealment, blinding of participants, blinding of personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. As many reports of randomized controlled trials published in Chinese journals lacked an adequate description of randomization sequence generation and allocation concealment,\textsuperscript{21} we will retrieve related protocols in clinical trials registration websites and contact first author/s or corresponding author/s through E-mail or telephone for further details of these two domains.

**Strategy for data synthesis and statistical analysis**

We will use RevMan 5.3 software for data analysis. For continuous data collected using the same measurement scale, we will calculate weighted mean difference (WMD) and 95% confidence intervals (CIs). For continuous data collected using similar measurement scales for the same outcome, we will calculate standardized mean differences (SMD) with 95% CIs. For dichotomous outcomes, we will use risk ratio (RR) with 95% CI and $p$ values to assess the efficacy and safety of CHM. A standard chi-squared statistic and $I^2$ statistic will be used to test heterogeneity between groups. Data will be analyzed with a fixed-effect model if no statistical heterogeneity was observed between subgroups ($P \geq 0.1$, $I^2 \leq 50\%$). In the presence of heterogeneity ($P < 0.1$, $I^2 > 50\%$), a random-effect model will be used and the possible causes of heterogeneity will be examined.

**Dealing with missing data or unclear scale type**

We will attempt to contact the authors of included studies in which there is missing data or unclear source of the evaluation scales through e-mail or telephone. For missing data, if we fail to obtain sufficient data after contacting authors, an intention-to-treat analysis will be performed if feasible.

**Planned subgroup analyses**

Where possible we will perform subgroup analyses based on different demographic characteristics or vascular risk factors, severity of included patients, different disease
durations, diagnostic criteria, intervention type (CHM or CHM in combination with routine pharmacotherapy), routes of administration, dosage, preparations and ingredients of CHM interventions and controls.

**Sensitivity analysis**
Where feasible, we will carry out sensitivity analyses to investigate the robustness of the study conclusions, such as grouping studies by different levels of the methodological quality.

**Assessment of publication biases**
We will use funnel plots in RevMan 5.3 and Egger’s test in Stata 11.0 to detect publication bias if more than 10 studies are included in the meta-analysis.

**Assessment of Quality of Evidence**
The Cochrane Collaboration Network GRADE (The Grading of Recommendations Assessment Development and Evaluation) will be used to assess the results in this systematic review. We will create a Summary of Finding (SoF) table in http://www.guidelinedevelopment.org/.

**Ethics and dissemination**
Ethical approval will not be required for this systematic review because there are no concerns regarding patient’s privacy. The results will be disseminated in a peer-reviewed journal and presented at a relevant conference.

**DISCUSSION**
VCIND belongs to the categories of Jianwang, Shanwang, Daibing in traditional Chinese medicine. CHMs have been cited for treating memory disorders in the classical herbal literature for many centuries and the results of pre-clinical and clinical studies suggest that CHM could improve cognitive decline. For example, Ginkgo biloba extract EGb 761 is the most extensively clinically tested Chinese herbal-based substance for cognitive impairment and dementia and meta-analytic evidence suggests that EGb 761 provides benefit for stabilizing or slowing decline in cognition of people with cognitive impairment and dementia. Huperzine A is another Chinese herbal derivative which has been authorized for treating Alzheimer’s disease (AD) and benign memory deficits since 1994 in China. As an alkaloid
isolated from the Chinese herb *Huperzia serrata*, Huperzine A can selectively inhibit acetylcholinesterase activity and thus facilitate the increase in acetylcholine level in the brain thereby improving cognitive function in patients with dementia.\textsuperscript{28} Meta-analysis also shows Huperzine A could significantly improve the MMSE and ADL score of AD and VD patients with a good tolerance.\textsuperscript{28} But there is, as yet, no overall assessment of the clinical evidence regarding CHM interventions for VCIND in evidence-based medicine.

Thus, we plan to conduct this meta-analysis to evaluate the efficacy and safety of Chinese herbal medicine therapies for patients with VCIND. We hope that this review will provide evidence to assist clinicians and patients’ decision-making process when dealing with VCIND. However, No internationally recognized VCIND diagnostic criteria currently exist. This will be a potential source of heterogeneity for the included study population and influence the extrapolation of conclusion. Therefore, subgroup analyses according to the characteristic of VCIND and different diagnosis criteria will need to be carried out.

Appendix 1: Search strategy used in PubMed database.

Appendix 2: PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol.\textsuperscript{29}

**Contributors**

Chuanjian Lu, Charlie Changli Xue, Xinfeng Guo and Anthony Lin Zhang conceived and designed the study. The manuscript of this protocol was drafted by Mei Feng, Jingmin Lu and Brian H. May and revised by Chuanjian Lu and Charlie Changli Xue.

Mei Feng, Jingmin Lu designed search strategies and will perform the search, screening and assessment of the risk of bias independently. Mei Feng and Brian H. May will analyse and interpret the data. Shaonan Liu will arbitrate any disagreements during the review. All authors approved the final version of this protocol.

**Competing interests:** None.
Funding: This study is funded by a Project Grant from the Guangdong Provincial Science & Technology Department and the Guangdong Provincial Academy of Chinese Medical Sciences (GPACMS) (Project Grant no. 2012A032500009). The study is partially supported by a Grant from the International Science & Technology Cooperation Project of the Ministry of Science and Technology of China (Project Grant no. 2012DFA31760) and International Science and Technology Cooperation Project of TCM funded by State Administration of TCM, China (Project Grant no.160150000027〔11〕).

REFERENCES


Table 1  Summary of primary outcome assessments

<table>
<thead>
<tr>
<th>Outcome categories</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Function</td>
<td>• MMSE (Mini Mental Status Examination)</td>
</tr>
<tr>
<td></td>
<td>• HDS (Hasagawa Dementia Scale)</td>
</tr>
<tr>
<td></td>
<td>• ADAS-cog (Alzheimer’s disease assessment scale-cognitive)</td>
</tr>
<tr>
<td></td>
<td>• MoCA (Montreal Cognitive Assessment)</td>
</tr>
<tr>
<td></td>
<td>• WMS (Wechsler Memory Scale)</td>
</tr>
<tr>
<td>Activities of Daily Living</td>
<td>• Activities of Daily Living</td>
</tr>
<tr>
<td></td>
<td>• ADCS-ADL (Alzheimer disease cooperative study-ADL inventory)</td>
</tr>
<tr>
<td></td>
<td>• FAQ (Functional activity questionnaire)</td>
</tr>
<tr>
<td>Behavioral and Psychological Symptoms of Dementia (BPSD)</td>
<td>• NPI (neuropsychiatric inventory)</td>
</tr>
<tr>
<td></td>
<td>• HAMD (Hamilton depression scale)</td>
</tr>
<tr>
<td></td>
<td>• CSDD (Cornell scale for depression in dementia)</td>
</tr>
<tr>
<td>Global Evaluation</td>
<td>• CDR (clinical dementia rating)</td>
</tr>
<tr>
<td></td>
<td>• CIBIC-plus (clinicians’ interview-based impression of change-plus)</td>
</tr>
<tr>
<td></td>
<td>• GDS (global deteriorate scale)</td>
</tr>
</tbody>
</table>
### Table 2  Search strategy used in PubMed database

<table>
<thead>
<tr>
<th>No</th>
<th>Search terms</th>
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<tbody>
<tr>
<td>1</td>
<td>vascular cognitive impairment</td>
</tr>
<tr>
<td>2</td>
<td>mild cognitive impairment</td>
</tr>
<tr>
<td>3</td>
<td>post-stroke cognitive impairment</td>
</tr>
<tr>
<td>4</td>
<td>VCI</td>
</tr>
<tr>
<td>5</td>
<td>or 1–4</td>
</tr>
<tr>
<td>6</td>
<td>Medicine, Chinese Traditional</td>
</tr>
<tr>
<td>7</td>
<td>Drugs, Chinese Herbal</td>
</tr>
<tr>
<td>8</td>
<td>herbal medicine</td>
</tr>
<tr>
<td>9</td>
<td>Chinese traditional medicine</td>
</tr>
<tr>
<td>10</td>
<td>Traditional Chinese medicine</td>
</tr>
<tr>
<td>11</td>
<td>or 6–10</td>
</tr>
<tr>
<td>12</td>
<td>5 and 11</td>
</tr>
</tbody>
</table>

This search strategy will be modified as required for other electronic databases.
Appendix 1: Search strategy used in PubMed database

#1 vascular cognitive impairment

#2 mild cognitive impairment

#3 post-stroke cognitive impairment

#4 VCI

#5 #1 or #2 or #3 or #4

#6 Medicine, Chinese Traditional

#7 Drugs, Chinese Herbal

#8 herbal medicine

#9 Chinese traditional medicine

#10 Traditional Chinese medicine

#11 #6 or #7 or #8 or #9 or #10

#12 #5 and #11
### Appendix 2

**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol [29]**

<table>
<thead>
<tr>
<th>Section and topic</th>
<th>Item No</th>
<th>Checklist item</th>
<th>Reported on page</th>
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<tr>
<td><strong>ADMINISTRATIVE INFORMATION</strong></td>
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<td></td>
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<td>Title:</td>
<td>Identification 1a</td>
<td>Identify the report as a protocol of a systematic review</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Update 1b</td>
<td>If the protocol is for an update of a previous systematic review, identify as such</td>
<td>Not an update</td>
</tr>
<tr>
<td>Registration</td>
<td>2</td>
<td>If registered, provide the name of the registry (such as PROSPERO) and registration number</td>
<td>2</td>
</tr>
<tr>
<td>Authors:</td>
<td>Contact 3a</td>
<td>Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Contributions 3b</td>
<td>Describe contributions of protocol authors and identify the guarantor of the review</td>
<td>8</td>
</tr>
<tr>
<td>Amendments</td>
<td>4</td>
<td>If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments</td>
<td></td>
</tr>
<tr>
<td>Support:</td>
<td>Sources 5a</td>
<td>Indicate sources of financial or other support for the review</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Sponsor 5b</td>
<td>Provide name for the review funder and/or sponsor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Role of sponsor or funder 5c</td>
<td>Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol</td>
<td></td>
</tr>
<tr>
<td><strong>INTRODUCTION</strong></td>
<td>6</td>
<td>Describe the rationale for the review in the context of what is already known</td>
<td>2-3</td>
</tr>
<tr>
<td>Objectives</td>
<td>7</td>
<td>Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)</td>
<td>3</td>
</tr>
<tr>
<td><strong>METHODS</strong></td>
<td>8</td>
<td>Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review</td>
<td>3-4</td>
</tr>
<tr>
<td>Information sources</td>
<td>9</td>
<td>Describe all intended information sources (such as electronic databases, contact with study authors, trial</td>
<td>4-6</td>
</tr>
<tr>
<td>Search strategy</td>
<td>10</td>
<td>Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated</td>
<td>5, 13</td>
</tr>
<tr>
<td>-----------------</td>
<td>----</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Study records:</td>
<td>11a</td>
<td>Describe the mechanism(s) that will be used to manage records and data throughout the review</td>
<td>5</td>
</tr>
<tr>
<td>Selection process</td>
<td>11b</td>
<td>State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)</td>
<td>5</td>
</tr>
<tr>
<td>Data collection process</td>
<td>11c</td>
<td>Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators</td>
<td>5</td>
</tr>
<tr>
<td>Data items</td>
<td>12</td>
<td>List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications</td>
<td>5</td>
</tr>
<tr>
<td>Outcomes and prioritization</td>
<td>13</td>
<td>List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale</td>
<td>4, 12</td>
</tr>
<tr>
<td>Risk of bias in individual studies</td>
<td>14</td>
<td>Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis</td>
<td>5-6</td>
</tr>
<tr>
<td>Data synthesis</td>
<td>15a</td>
<td>Describe criteria under which study data will be quantitatively synthesised</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>15b</td>
<td>If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I², Kendall’s τ)</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>15c</td>
<td>Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)</td>
<td>6-7</td>
</tr>
<tr>
<td></td>
<td>15d</td>
<td>If quantitative synthesis is not appropriate, describe the type of summary planned</td>
<td>6</td>
</tr>
<tr>
<td>Meta-bias(es)</td>
<td>16</td>
<td>Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)</td>
<td>7</td>
</tr>
<tr>
<td>Confidence in cumulative evidence</td>
<td>17</td>
<td>Describe how the strength of the body of evidence will be assessed (such as GRADE)</td>
<td>7</td>
</tr>
</tbody>
</table>
Chinese herbal medicine for patients with vascular cognitive impairment no dementia: protocol for a systematic review

Mei Feng, Jingmin Lu, Brian H May, Shaonan Liu, Xinfeng Guo, Anthony Lin Zhang, Charlie Changli Xue and Chuanjian Lu

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