Association between chronic cerebrospinal venous insufficiency and multiple sclerosis: a systematic review and meta-analysis

Jun Yang, Na Zhang, Cong Ding, Xiuying He, Meihua Li, Wei Meng, Taohui Ouyang

ABSTRACT

Objectives Numerous studies have indicated that chronic cerebrospinal venous insufficiency is a potential factor in causing multiple sclerosis in recent years, but this conclusion remains unconfirmed. This meta-analysis examined the correlation between chronic cerebrospinal venous insufficiency and chronic cerebrospinal venous insufficiency.

Methods We searched Embase and Medline (Ovid) for publications from 1 January 2006 to 1 May 2022. The meta-analysis was performed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Results Eligible studies (n=20) included 3069 participants from seven countries. Pooled analysis indicated that chronic cerebrospinal venous insufficiency was more frequent in patients with multiple sclerosis than in healthy controls (OR 3.36; 95% CI 1.92 to 5.85; p<0.001) with remarkable heterogeneity among studies (I²=79%). Results were more strongly correlated in subsequent sensitivity analyses, but heterogeneity was also more substantial. We removed studies that initially proposed a chronic cerebrospinal venous insufficiency team as we as studies by authors involved in or advocating endovascular therapies.

Conclusions Chronic cerebrospinal venous insufficiency is significantly associated with multiple sclerosis and it is more prevalent in patients with multiple sclerosis than in healthy individuals, but considerable heterogeneity of results is still observed.

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory condition of the central nervous system of unknown cause, and most findings suggest that the reason is autoimmune pathology. Chronic cerebrospinal venous insufficiency (CCSVI) is a syndrome characterised by multiple stenosis or obstruction of intracranial and extracranial veins, which results in inadequate cerebral venous drainage. In 2008, Zamboni et al suggested that CCSVI could potentially cause MS. This hypothesis assumed that multiple stenoses or obstructions of the veins, which in turn affect the extracranial outflow channels of the cerebral venous system (internal jugular and ayzyous veins), eventually lead to an increase in intracranial pressure, followed by blood–brain barrier rupture, local iron deposition and triggering of the inflammatory chain in MS. This abnormal venous drainage can be diagnosed by Doppler ultrasound, MRI, cerebral perfusion studies and catheter venography. However, the so-called Zamboni criterion is the most widely used detection mode, and the operation is non-invasive. Zamboni et al defined five ultrasound criteria for diagnosing CCSVI by transcranial and extracranial echocardiography Doppler in a study, which revealed that patients had CCSVI when two or more abnormal ultrasound parameters were observed. These five ultrasound parameter criteria include (1) reflux in the internal jugular and/or vertebral veins in the supine and sitting positions; (2) reflux in the deep cerebral veins; (3) high-resolution B-mode evidence of internal jugular vein stenoses; (4) flow is not Doppler detectable in the internal jugular and/or vertebral veins; (5) reverted postural control of the main cerebral venous outflow route measured in internal jugular veins.

Since then, most investigators have used this criterion to diagnose patients with CCSVI, but
the evaluation results of the correlation between CCSVI and MS were inconsistent across studies. Coupled with the fact that despite the availability of neuroimaging techniques such as magnetic resonance venogram or selective venography to assess abnormal central system venous drainage, the pathogenic role of CCSVI in MS remains unproven. In addition, the possibility of CCSVI therapy has been a topic of conversation, including intravenous percutaneous transluminal angioplasty (termed ‘liberation treatment’) proposed by Zamboni et al. This treatment has received widespread attention from patients with MS and scientific institutions worldwide. Still, there are articles reporting its potential adverse consequences. Although the follow-up clinical trials showed that venous angioplasty was relatively safe, it did not play an ideal therapeutic effect for patients with MS. The lack of sufficient proof that CCSVI is connected to MS has called into question the idea of intravenous percutaneous transluminal angioplasty, especially given the various research results and associated negative side effects. To evaluate whether CCSVI was connected with MS and whether its frequency varied between patients with MS and healthy controls, this study did a thorough meta-analysis by pooling studies on the connection of CCSVI with MS. Furthermore, sensitivity analyses were used to investigate potential explanations for heterogeneity.

MATERIALS AND METHODS

Literature search

This meta-analysis was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guidelines. The specific PROSPERO protocol process is placed in the online supplemental file 2. Two authors independently searched the Medline versus Embase databases using the Ovid portal, with search dates adjusted from 1 January 2006 to 1 May 2022. Disagreements between the two authors’ searches were resolved by a third-party reviewer. The complete search strategy for this study can be found in the online supplemental appendix 1. Search terms included: “Multiple Sclerosis” and “Ultrasound”. The search findings were restricted to English-language articles and human studies. Following that, we critically reviewed all publications that fit these parameters and conducted manual searches of their references and citations of relevant reviews to search for research outside the database. If data were missing or erroneous, the researchers contacted the author again.

Eligibility

The inclusion criteria were as follows: (1) English language, (2) use of Doppler ultrasound to detect CCSVI, (3) neurological testing criteria used to identify CCSVI, (4) inclusion of at least one control group and (5) blinding of study. Exclusion criteria were: (1) no raw data or incomplete data, (2) overlapping data (the study with the complete data chosen for the series of the same author and pattern), (3) literature of too low quality or literature not available in full text, and (4) less than 10 cases or control subjects. After deleting duplicates, two researchers independently read the titles and abstracts of all identified papers, read the full-text versions, compared the results and resolved discrepancies by a consensus.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Data extraction

Two authors extracted data and entered them into a standardised collection form, independently reviewed and confirmed by a third author. The extracted data were as follows: first author, country, publication date, sample size, demographic characteristics of participants (age vs percentage female) and study characteristics of patients (disease duration, percentage treated and Expanded Disability Status Scale). For some of the missing data, the researchers were also active in obtaining them from the article’s authors via email.

Quality assessment

All 20 studies used the Newcastle–Ottawa Quality Assessment Scale to assess the risk of bias. The scale is based on case–control studies and consists of three domains: selection, comparability and exposure, with quality ratings ranging from 0 to 9. Four study items are in the selection domain, each given a maximum of one star. Three study items are in the exposure category, each given at least one star. For comparability, only one item is included, and a maximum of two stars is presented. We consider this high-quality literature with low bias if at least seven stars are awarded.

Statistical analyses

STATA V.17.0 (StataCorp, College Station, Texas, USA) was used to conduct the meta-analysis by the researchers. One investigator entered the detailed data into the software. Another investigator reviewed the data for accuracy, generating forest plots and OR to determine whether there was a statistical relevance between CCSVI and MS. We used either a random-effects or fixed-effects model for the meta-analysis. A random-effects model was selected if the results showed significant heterogeneity ($I^2 > 50\%$). An OR greater than 1.0 in the results indicated that CCSVI could be a potential risk factor for MS. P values of $< 0.05$ were considered statistically significant. The origins of heterogeneity in the included studies were examined using Cochran’s Q and $I^2$ statistics. $I^2$ values of $50\%$–$90\%$ represent substantial heterogeneity, while at least $75\%$ represent considerable heterogeneity. By the Cochrane Review Manager version 5.4.1, for publication bias was assessed using Egger’s test ($p<0.05$ indicates significant publication bias). If the results indicated the presence of publication bias, the fill-and-trim methods were used to detect publication bias. To determine the

RESULTS

Included studies
The selection process of the study is shown in figure 1. During the initial search, 2544 studies were located, with 1910 records from the Embase database, 634 from the Medline database and no additional records. After removing 468 duplicate studies, 2076 publications were included in the title and abstract screening, and 58 were selected for full-text filtering. After full-text screening and checking, 38 of these articles were excluded: 10 examined irrelevant focus, 18 assessed veins in other ways, 1 without a control group, 5 did not use blinding, 1 used duplicate data, 2 used overlapping and 1 had incomplete experimental data. Ultimately, 20 studies met the eligibility criteria (figure 1).

Study characteristics
Of the currently incorporated studies, 11 were conducted in Italy, 3 in the USA, 2 in Germany, 1 in Canada, 1 in Denmark, 1 in the Netherlands and 1 in Turkey (table 1). It is noteworthy that the included studies were conducted in Europe or North America. This study included healthy controls (table 1). All the studies used Doppler ultrasonography to detect CCSVI. Two studies did not report an assessment of the five ultrasound parameters of the CCSVI, and three studies reported only four estimates because the investigators were unable to perform the full five-item neurological protocol. Although eight papers covered ultrasound technology training, they did not describe in detail the procedures and quality of the training (table 1). Four ultrasound investigators have participated in CCSVI endovascular treatment clinical trials or studies supporting liberation procedures.

In terms of blinding, 8 reports explained the blinding poorly but described the process more entirely in 12 studies, expressed it well in 2 of them and reported success with blinding (table 1). Five studies described intraobserver variability. Nevertheless, only four ultrasound investigators described good intraobserver and interobserver reliability in a run-in period. The experimental group in five studies was not age and gender matched to the control group (see online supplemental table 1).

In the study by Zamboni et al, there was also no separate discussion about the outcome in healthy individuals. Regarding the disease type of MS, relapsing-remitting MS was still dominant, with primary progressive MS and secondary progressive MS in second place (see online supplemental table 2). Six studies reported clinically isolated syndromes in patients, and all patients with MS had clinically isolated syndrome in the survey by Baracchini et al (see online supplemental table 2). Furthermore, most patients received varying degrees of treatment, with acceptance rates ranging from 28% to 90% (see online supplemental table 2). Females were more prevalent in the experimental groups than in the control groups, with percentages ranging from 16.7% to 82.1% in the experimental groups and 36.4% to 75.0% in the control groups. Online supplemental table 2 summarises the data for patients with MS for age, the proportion of females, duration of disease and Expanded Disability Status Scale scores. These data are typical of patients with MS.

Risk of quality assessment
All 20 studies were included in the Newcastle–Ottawa Quality Assessment Scale, and all had a good quality rating result. Fifteen studies had a quality rating of greater than or equal to seven and were considered high-quality studies. None of the incorporated studies were categorised as low quality with a high risk of bias assessment (see online supplemental table 3).

Pooling of studies
In further studies, figure 2 presents the meta-analysis results of the association of CCSVI with MS and the incidence of CCSVI in MS versus healthy controls. Twenty studies reported the incidence of CCSVI, with a significant difference in the incidence of CCSVI in MS.
<table>
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<th>Study</th>
<th>Country</th>
<th>MS cases (n)</th>
<th>Controls (n)</th>
<th>Blinding</th>
<th>Receive appropriate training in ultrasound operation</th>
<th>Involved in ‘liberation procedure’</th>
<th>The way patients were identified for enrolment</th>
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<td>Marder et al&lt;sup&gt;26&lt;/sup&gt;</td>
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<td>11</td>
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<td>No</td>
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Continued
compared with healthy controls. In Zamboni et al's study, three studies had an incidence of 0, reaching 100%. There remained a wide variation in the strength of the association between CCSVI and MS. More specifically, the ORs ranged from 0.32 (95% CI: 0.01 to 8.26) in Mayer et al's study to 58035.00 (95% CI: 1142.20 to 2948755.78) in Zamboni et al's research. According to the pooled analysis, CCSVI and MS were remarkably correlated (OR 3.36; 95% CI: 1.92 to 5.85; p<0.001). However, there was extensive heterogeneity among the studies (I²=79%).

**Publication bias**

The Egger's test was employed to analyse publication bias, and its results showed no significant publication bias (t=1.22, p=0.241). Therefore, there is no need to use the fill-and-trim methods for further analysis.

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**Table 1** Continued

<table>
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<th>Study</th>
<th>Country</th>
<th>MS cases (n)</th>
<th>Controls (n)</th>
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<th>Receive appropriate training in ultrasound operation</th>
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</table>

n, number.

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**Figure 2** Meta-analysis of the probability of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis versus healthy controls.
Sensitivity analyses
The sensitivity analysis results demonstrated that the combined effect sizes were not affected by the effects of any single study, suggesting good stability of the meta-analysis results (see online supplemental appendix 3).

Subgroup analysis
Since Zamboni et al were overly aggressive in their studies on CCSVI (n=11), additional subgroup analyses were performed by removing studies about Zamboni’s team and those that had previously been conducted with that team (n=7). Although patients with MS had CCSVI at a higher rate than controls, the correlation between CCSVI and MS was diminished (OR 2.83; 95% CI: 1.46 to 5.48, p<0.05; figure 3) and remained strongly heterogeneous (I²=56%). On the other hand, the correlation between the two was stronger (OR 4.11; 95% CI: 1.62 to 10.39, p<0.001; figure 3), and the heterogeneity was more pronounced in the seven excluded studies (I²=89.4%).

In the following sensitivity analysis, considering the potential conflicts of interest between the studies, we deleted articles by authors involved in CCSVI endovascular treatment clinical trials or studies supporting liberation procedures (n=4). There was no substantial change in outcome, a diminished correlation (OR 2.87; 95% CI: 1.82 to 4.52; p<0.05; figure 4), and heterogeneity remained significant (I²=54.4%). In contrast, a more significant correlation was obtained for those studies assessed in support of liberation therapy authors (OR 17.05; 95% CI: 1.27 to 229.53; p<0.0001; figure 4), along with more significant heterogeneity (I²=96.1%).

DISCUSSION
This meta-analysis revealed a statistically significant relationship between CCSVI and MS and a wide range of heterogeneity. In a subsequent sensitivity analysis, the results showed that the combined effect size was not affected by any single study. We also performed subgroup analyses to seek sources of heterogeneity, but none of the results were satisfactory.

The meta-analysis also found that patients with MS had a higher prevalence of CCSVI than healthy groups, but it varied considerably across studies. On the other hand, however, we could not confirm what factors led to the significant differences in incidence between the studies. One of these possibilities is the ultrasound detection aspect. Many studies have shown that the quality level of Doppler ultrasound for diagnosing CCSVI depends on the operator and that trained operators perform better in reproducibility. This imaging technique is more difficult when testing veins at low-pressure flow, and the dehydrated state of the subject and head rotation contribute to the poor quality of the results. Of all
included studies, only eight articles had relevant operator training. For consistency of operation, performance was equally poor, where only five included studies were evaluated and four showed good agreement. These data further suggest that the reproducibility of CCSVI diagnostics requires additional studies while emphasising the importance of relevant operator training in the skills.

Ultrasound detection of the intracranial cerebral venous system is the most challenging part. On the one hand, the cerebral vein detection procedure is complex and usually studied through a transcranial approach, taking either a temporal window or a transoccipital approach. Although both provide better information on blood flow, detecting venous abnormalities is difficult. Due to the skull, the intracranial veins are not regulated by the respiratory pump as the extracranial veins usually are. Furthermore, 17 of the surveyed studies conducted transcranial testing, while the other 2 used a transtemporal and transoccipital approach without detailing the modality used for the remaining. On the other hand, all included studies were performed in the context of a potential association between multiple sclerosis and CCSVI. However, when examined from an objective perspective, it seems more accurate to test the validity of a test versus a test using an established gold standard rather than focusing on the presence or absence of MS. This suggests that the five neurological tests proposed by Zamboni et al are questionable, such as vascular stenosis, internal jugular vein cross-sectional area differences or reflux which are challenging to detect objectively by these criteria. Therefore, the relationship between CCSVI and MS still needs more studies and uniform standards to be validated.

In addition, MRI, catheter venography and intravascular ultrasound are noteworthy in detecting the true prevalence of CCSVI, although the latter two are invasive procedures. The International Society for Neurovascular Disease has recommended a multimodality combination of invasive and non-invasive testing for extracranial venous anomalies to achieve optimal detection in patients of interest. Specifically, at least one invasive detection technique and at least one non-invasive detection technique should be used.

Although CCSVI is thought to be associated with cerebral venous abnormalities, the aetiology of cerebral venous abnormalities and the possible pathophysiological link to MS and other neurological disorders remain unclear. Several studies have suggested that, in the setting of venous flow abnormalities, this potential association is related to the accumulation of leucocytes in the vasculature.
Interestingly, this study contradicts a previous meta-analysis, which showed reduced heterogeneity after removing publications related to the liberation procedures (I²=57.3%). In contrast, considerable heterogeneity was still observed after the same manipulation in this paper (I²=54.4%), which may be due to inconsistent inclusion criteria for both studies. Although both included studies used neurological criteria, Tsivgoulis et al included non-blinded studies as well as reports from experimental groups with fewer than 10 cases, leading to a final inclusion of demographics varying widely and inconsistent sensitivity analysis results. On the other hand, prior to the writing of this article, four meta-analyses had discussed the association between CCSVI and MS, but only one had reached a definitive conclusion. We need to be aware that the conclusions of previous meta-analyses influence the methodology and even the results of subsequent clinical trials, which then accumulate to trigger accumulation bias. Overly optimistic initial studies or meta-analyses can inspire additional studies, while disappointing results can bring a series of studies to an end. Although we attempted to attenuate the effect of prior studies in our subgroup analysis (removing studies from the Zamboni-related teams), the final results were similar to the initial results. Attempts to eliminate such biases seem unrealistic because new research is continually inspired by previous research and may trigger more unnecessary research waste in the process of elimination. Although bias elimination is unavoidable, meaningful error control can be performed. One study has shown that the likelihood ratio is a valid test. In future clinical trials or meta-analyses, researchers should be aware of the accumulation bias of previous studies.

LIMITATION

The current meta-analysis has some limitations that must be taken into account. First, we searched only two databases in this analysis; a lack of access to more databases and a lack of high-quality literature limited our further analysis. Second, some of the included studies had inferior descriptions of blinding and limited descriptions of ultrasonography, so we could not explore whether inconsistencies in blinding or differences in ultrasound protocols between studies contributed to the heterogeneity in the studies. Furthermore, six studies also included groups without MS with other neurological disorders. In the current study, we included only healthy controls. We did not acquire the data of the individuals in the study, and there were considerable age and sex differences between the studies, coupled with the fact that five reports did not have controls of the same age and sex as the patients with MS, so it was impossible to determine whether demographic factors influenced the morbidity of CCSVI in controls and patients with MS. More critically, the topic of CCSVI versus MS remains controversial. Studies may be published regardless of the examination method or whether they are positively or negatively evaluated. Finally, the inconsistent diagnostic criteria for screening patients with MS across studies and the lack of reliable evidence in the text to determine the diagnosis of subjects made it impossible to judge the accuracy of the experimental versus control groups.

CONCLUSIONS

In summary, the present meta-analysis exhibited a strong correlation between CCSVI and MS, while CCSVI was more likely to occur in patients with MS than in healthy controls. CCSVI may be a potential risk factor for MS. Nevertheless, the heterogeneity was highly significant that we cannot draw clear conclusions. Future studies of higher quality, especially in terms of blinded quality and reproducibility of ultrasound diagnosis, are still needed to derive a deeper discussion of the association of CCSVI with MS.

ACKNOWLEDGEMENTS

We are very grateful to Chole Fu and Dr Liu for their support and assistance in this study.

CONTRIBUTORS

JY was the first author. NZ received funding. TO and JY designed the study. WM and ML collected the data. XH participated in data verification. CD analysed the data. JY drafted the manuscript. TO and NZ participated in the interpretation of the results and critical revision of important intellectual content of the manuscript and approved the final version of the manuscript. All authors have read and approved the final manuscript. WM and ML were the guarantors of the study.

FUNDING

This study was supported by grants from the National Natural Science Foundation of China (81960247).

COMPETING INTERESTS

None declared.

PATIENT AND PUBLIC INVOLVEMENT

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

PATIENT CONSENT FOR PUBLICATION

Not required.

ETHICS APPROVAL

This study does not involve human participants; thus, ethical approval was not required.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

DATA AVAILABILITY STATEMENT

Data are available upon reasonable request. All data in this article were available from included studies and were provided by the authors without reservation.

SUPPLEMENTAL MATERIAL

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REFERENCES

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Supplementary Appendix 1: Detailed literature search

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<th>MEDLINE (OVID) Search Strategy</th>
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<tr>
<td>9 (multiple adj sclerosis).mp.</td>
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<tr>
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<td>9 ADEM.tw.</td>
</tr>
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<td>10 Optic Neuritis/</td>
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<td>11 (optic adj neuritis$).tw.</td>
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<tr>
<td>13 devic.tw.</td>
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<tr>
<td>14 &quot;clinically isolated syndrome&quot;?.tw.</td>
<td>13 encephalomyelitis.tw.</td>
</tr>
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<td>14 devic.tw.</td>
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<td>15 &quot;clinically isolated syndrome&quot;?.tw.</td>
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<td>16 Demyelinating Disease/</td>
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<td>21 Doppler$.mp.</td>
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</tr>
<tr>
<td>25 Cerebral Angiography/</td>
<td>24 &quot;magnetic resonance arteriogra$&quot;.tw.</td>
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<td>26 (cerebral adj angiogra$).tw.</td>
<td>25 exp brain angiography/</td>
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<tr>
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<td>38</td>
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<tr>
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<tr>
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**Table e1** Characteristics of participants included in controls.

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<tr>
<th>Study</th>
<th>Participants (n)</th>
<th>Age (year)</th>
<th>Female (%)</th>
<th>Controls matched to cases on sex and age</th>
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<tr>
<td>Zivadinov et al</td>
<td>163</td>
<td>50 †</td>
<td>73.1</td>
<td>No</td>
</tr>
<tr>
<td>Tromba et al</td>
<td>67</td>
<td>32 *</td>
<td>49.3</td>
<td>No</td>
</tr>
<tr>
<td>Leone et al</td>
<td>68</td>
<td>40 *</td>
<td>64.7</td>
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</tr>
<tr>
<td>Cardaioli et al</td>
<td>18</td>
<td>31 *</td>
<td>66.7</td>
<td>No</td>
</tr>
<tr>
<td>Imperiale et al</td>
<td>41</td>
<td>45 *</td>
<td>56.1</td>
<td>Yes</td>
</tr>
<tr>
<td>Mayer et al</td>
<td>20</td>
<td>34 *</td>
<td>50.0</td>
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<tr>
<td>Baracchini et al</td>
<td>60</td>
<td>46 *</td>
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<td>Costello et al</td>
<td>60</td>
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<td>75.0</td>
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<tr>
<td>Van den Berg et al</td>
<td>41</td>
<td>44 †</td>
<td>48.8</td>
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</tr>
<tr>
<td>Patti et al</td>
<td>172</td>
<td>43 *</td>
<td>58.1</td>
<td>Yes</td>
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<td>Baracchini et al</td>
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<td></td>
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<tr>
<td>Group 2 §</td>
<td>60</td>
<td>63 *</td>
<td>53.3</td>
<td></td>
</tr>
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<td>Gandhi et al</td>
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<td>Zamboni et al</td>
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<td>73.0</td>
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<td>Caprio et al</td>
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<td>Amato et al</td>
<td>16</td>
<td>18 †</td>
<td>44.0</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Note. *: mean. †: median.
‡: Healthy controls in group 1 were matched with MS patients.
§: In the study by Baracchini et al., healthy controls in group 2 were matched with controls who had neurologic diseases other than MS; in the study by Zamboni et al., healthy controls in group 2 were older than the median age of the European MS population.
<table>
<thead>
<tr>
<th>Study</th>
<th>Patients with MS (n)</th>
<th>Age (year)</th>
<th>Proportion of female (%)</th>
<th>Duration of MS</th>
<th>Receive treatment (%)</th>
<th>EDSS score</th>
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<td>RRMS 30</td>
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<td>4</td>
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<td>56</td>
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<td>0</td>
<td>0</td>
<td>37 *</td>
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</tbody>
</table>

Note. n = number; NA = not applicable; EDSS = Expanded Disability Status Scale; CIS = Clinically isolated syndrome; RRMS = Relapsing remitting MS; SPMS = secondary progressive MS; PPMS = primary progressive MS.

*: mean.

†: median.
### Table E3: Results of quality assessment using the Newcastle–Ottawa Scale.

<table>
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<tr>
<th>Study</th>
<th>Selection</th>
<th>Comparability</th>
<th>Exposure</th>
<th>Scores (0–9)</th>
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<td>Selection of controls</td>
<td>Definition of controls</td>
<td>Comparability of cases and controls on the basis of the design or analysis</td>
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<td>*</td>
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<td>*</td>
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<td>Tromba et al(^z^3)</td>
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<td>*</td>
<td>*</td>
<td>**</td>
</tr>
<tr>
<td>Leone et al(^z^8)</td>
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<td>*</td>
<td>*</td>
<td>**</td>
</tr>
<tr>
<td>Cardioli et al(^z^4)</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>**</td>
</tr>
<tr>
<td>Imperiale et al(^z^2)</td>
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<td>*</td>
<td>*</td>
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<td>Mayer et al(^z^5)</td>
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<td>*</td>
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<td>Patti et al(^z^4)</td>
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<td>*</td>
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<tr>
<td>Baracchini et al(^z^8)</td>
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<td>*</td>
<td>*</td>
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<tr>
<td>Gandhi et al(^z^3)</td>
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<td>*</td>
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<td>Centonze et al(^z^3)</td>
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<td>*</td>
<td>*</td>
<td>**</td>
</tr>
<tr>
<td>Zamboni et al(^z^6)</td>
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<td>Marder et al(^z^6)</td>
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<td>Kantarcı et al(^z^9)</td>
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<td>Caprio et al(^z^5)</td>
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</table>

60
Supplementary Appendix 3

**Figure f1**  Sensitivity analysis of included studies resulted in a display of the estimated pooled effect size regarding the association of chronic cerebrospinal venous insufficiency with multiple sclerosis.
Systematic review

Fields that have an asterisk (*) next to them means that they must be answered. Word limits are provided for each section. You will be unable to submit the form if the word limits are exceeded for any section.
Registrant means the person filling out the form.

This record cannot be edited because it has been marked as out of scope

Give the title of the review in English
Relevance between chronic cerebrospinal venous insufficiency and multiple sclerosis: a systematic review and meta-analysis

2. Original language title.
For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

3. * Anticipated or actual start date.
Give the date the systematic review started or is expected to start.
12/10/2022

4. * Anticipated completion date.
Give the date by which the review is expected to be completed.
25/01/2023

5. * Stage of review at time of this submission.
This field uses answers to initial screening questions. It cannot be edited until after registration.
Tick the boxes to show which review tasks have been started and which have been completed.
Update this field each time any amendments are made to a published record.
# PROSPERO

## International prospective register of systematic reviews

The review has not yet started: No

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<td>Data analysis</td>
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<td>No</td>
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</tbody>
</table>

Provide any other relevant information about the stage of the review here.

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Jun Yang

**Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:**

Mr Yang

7. * Named contact email.

Give the electronic email address of the named contact.

1191815774@qq.com

8. Named contact address

Give the full institutional/organisational postal address for the named contact.

the First Affiliated Hospital of Nanchang University, Jiangxi Province, China

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

18779534691
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The First Affiliated Hospital of Nanchang University

Organisation web address:


Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.

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Mr Jun Yang. The First Affiliated Hospital of Nanchang University

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

the National Natural Science Foundation of China

Grant number(s)

State the funder, grant or award number and the date of award

81960247

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None


Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. NOTE: email and country must be completed for each person, unless you are amending a published record.


State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

Is the prevalence of chronic cerebrospinal venous insufficiency higher in patients with MS compared to healthy individuals? Is there an association between chronic cerebrospinal venous insufficiency and MS?
State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

The following bibliographic databases were searched the MEDLINE versus Embase databases using the OVID portal, with search dates adjusted from January 1, 2006, to April 1, 2022.

17. URL to search strategy.
Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search results.


Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete.

18. * Condition or domain being studied.
Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

Multiple Sclerosis (MS) is a chronic neurological disease that primarily affects the central nervous system (which includes the brain and spinal cord). The cause is unknown, and it is characterized by demyelination in pathology. Common symptoms include muscle paralysis, motor impairment, sensory impairment, vision problems, fatigue, etc. Currently, there is no cure and common treatment methods include...
Treatment methods vary depending on the cause, including physical therapy, medication, rehabilitation, nutritional therapy, etc.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

The trial included patients of any age with multiple sclerosis.

20. * Intervention(s), exposure(s).
Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

use of Doppler ultrasound to detect chronic cerebrospinal venous insufficiency?

21. * Comparator(s)/control.
Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

use of Doppler ultrasound to detect chronic cerebrospinal venous insufficiency?

22. * Types of study to be included.
Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

We have no restrictions on the types of study designs eligible for inclusion.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

24. * Main outcome(s).
Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

There is a correlation between xx and multiple sclerosis.

Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

25. * Additional outcome(s).
List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main
outcomes. Where there are no additional outcomes please state ‘None’ or ‘Not applicable’ as appropriate to the review.

chronic cerebrospinal venous insufficiency is more prevalent in patients with multiple sclerosis than in healthy individuals.

Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

Two authors extracted data and entered it into a standardized collection form, independently reviewed and confirmed by a third author. The extracted data were as follows: first author, country, publication date, sample size, demographic characteristics of participants (age vs. percentage female), and study characteristics of patients (dis-ease duration, percentage treated, and expanded disability status scale). For some of the missing data, the researchers were also active in obtaining it from the article's authors via email.


State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

Two reviewers will independently assess risk of bias based on the following domains from recommendations from the Cochrane handbook: 1. Adequate sequence generation; 2. Allocation concealment; 3. Blinding; 4. Incomplete outcome data and how it was addressed; 5. Selective reporting of the outcome; 6. Any other biases. results of bias assessment will be presented in a figure and a graph indicating low, high or unclear risk of bias for each of the 6 items in each trial. Sensitivity analysis will be conducted based on the bias assessment to assess robustness of results.


Describe the methods you plan to use to synthesise data. This must not be generic text but should be specific to your review and describe how the proposed approach will be applied to your data. If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

STATA 17.0 (STATA Corp., College Station, TX, USA) was used to conduct the meta-analysis by the researchers. One investigator entered the detailed data into the software. Another investigator reviewed the data for accuracy, generating forest plots and odds ratios (ORs) to determine whether there was a statistical relevance between CCSVI and MS. The pooled ORs for this study were derived using a random-effects model. An OR greater than 1.0 indicates that at least two ultrasound diagnostic criteria were met and displayed a positive correlation between CCSVI and MS, with p 0.05, indicating a statistically significant
difference. The origins of heterogeneity in the included studies were examined using Cochran’s Q and I²
statistics. I² values of at least 50% are usually considered to represent substantial heterogeneity, while
values of at least 75% indicate considerable heterogeneity. By the Cochrane Review Manager 5.4 version
5.4.1. for publication bias was assessed using the Egger test, p 0.05 indicates significant publication bias.
Meanwhile, the Fill and Trim methods were used to correct for publication bias. To determine the effect of
individual studies in the article on the experimental results, the researchers used a sensitivity analysis by
excluding individual studies. In addition, we used subgroup analysis to further look for sources of
heterogeneity.

29. * Analysis of subgroups or subsets.
State any planned investigation of ‘subgroups’. Be clear and specific about which type of study or
participant will be included in each group or covariate investigated. State the planned analytic approach.
Sensitivity analyses to assess the robustness of the results and subgroup analyses to determine whether the
summary effects are related to the clinical characteristics of the included trials are pre-specified. In addition,
sensitivity analyses will be performed to include only those trials that do not have any assessment bias. Two
subgroup analyses will also be performed. The first one assesses whether studies by authors associated
with the Zamboni team have an impact on the results; the second one examines whether liberation therapy
has an impact on the relevance of the results.

30. * Type and method of review.
Select the type of review, review method and health area from the lists below.

Type of review
Cost effectiveness
No
Diagnostic
No
Epidemiologic
No
Individual patient data (IPD) meta-analysis
No
Intervention
No
Living systematic review
No
Meta-analysis
Yes
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Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No
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Child health
No

Complementary therapies
No

COVID-19
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
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No
Obstetrics and gynaecology
No
Oral health
No
Palliative care
No
Perioperative care
No
Physiotherapy
No
Pregnancy and childbirth
No
Public health (including social determinants of health)
No
Rehabilitation
No
Respiratory disorders
No
Service delivery
No
Skin disorders
No
Social care
No
Surgery
No
Tropical Medicine
No
Urological
No
Wounds, injuries and accidents
No
Violence and abuse
No
31. Language.
Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English
There is not an English language summary

32. Country.
Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.
China

33. Other registration details.
Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.
If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.
No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.
Do you intend to publish the review on completion?
No

Give brief details of plans for communicating review findings?

36. Keywords.
Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are
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included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

multiple sclerosis; chronic cerebrospinal venous insufficiency; ultrasound; meta-analysis

37. Details of any existing review of the same topic by the same authors.
If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

38. * Current review status.
Update review status when the review is completed and when it is published. New registrations must be ongoing so this field is not editable for initial submission.

Please provide anticipated publication date
Review_Ongoing

39. Any additional information.
Provide any other information relevant to the registration of this review.

40. Details of final report/publication(s) or preprints if available.
Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission). List authors, title and journal details preferably in Vancouver format.

Give the link to the published review or preprint.