

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between chronic cerebrospinal venous insufficiency and multiple sclerosis: a systematic review and meta-analysis
AUTHORS	Yang, Jun; Zhang, Na; Ding, Cong; He, Xiuying; Li, Meihua; Meng, Wei; Ouyang, Taohui

VERSION 1 – REVIEW

REVIEWER	Simka, Marian University of Opole, Department of Anatomy
REVIEW RETURNED	24-Feb-2023

GENERAL COMMENTS	<p>The paper has been much improved; still some issues should be addressed before final acceptance;</p> <ol style="list-style-type: none"> 1. Title. From grammatical point of view the phrase “relevance between... “ is incorrect. Please change it to “Association between chronic....” 2. For the reader of this paper who is not familiar with this particular topic it would be still unclear what does actually mean the term CCSVI. Moreover, there is a common misunderstanding in the literature regarding this issue. It should be clearly stated that, for example: “Chronic cerebrospinal venous insufficiency (CCSVI) is a syndrome characterized by stenoses in the extracranial veins draining the brain, which results in compromised cerebral venous drainage” For reference see: https://d1wqtxts1xzle7.cloudfront.net/67179674/The_chronic_cerebrospinal_venous_insuffi20210505-19608-5oz99e.pdf?1620229394=&response-content-disposition=inline%3B+filename%3DThe_chronic_cerebrospinal_venous_insuffi.pdf&Expires=1677233948&Signature=aB6AWq3RQ7ohDhOhnhx5tpWz-ytlS95qLqN2xS4NbPXWQ2e4BPh2cx0lx1CkVB2MuJQOVTaUK6uFqxTDW~aZyF3-UBvYPQz22t4iGk22y0cMcHQKZglxp7nFaQQJXog5YeCmHgGgbdvKkOsEy2l6A8-7C1KOi1v9kZypalQKD4C61InCZPQmtnYSp1tj5Cvj~GHBZ4jUsp4YHI8Lxpg3-vCeg7v7KxHeU8~-W1~FKuKx-VDV50a0rHNpsnK6FdXwwSJKXV~N67EvoJE4ZbN59v1sU0kQm6Z5axO-LYNRH2S~nly7VNYW5KTmA9CrNsUyyGZmmiXPABsrHk8H0urEDQ__&Key-Pair-Id=APKAJLOHF5GGSLRBV4ZA Such an abnormal venous drainage can be diagnosed, for example by means of Doppler ultrasound, and hence the so-called Zamboni’s criteria represent the most widely used mode of detection. Yet, it can also be diagnosed using MR imaging, cerebral perfusion studies, and catheter venography (which is the most reliable diagnostic method, although invasive one: M Simka, et al.: Catheter venography for the assessment of internal jugular veins and azygous vein: Position statement by expert panel of the International Society for Neurovascular Disease. Vasa 2013; 42(3):168-176.) 3. Page 2/10, line 44. There should be probably “azygous vein” (no such thing as “odd vein” exists) 4. Page 2/10, line 61. Only one clinical trial on invasive treatment is cited and discussed. Actually, there were several such trials and overview of them has been published at: https://www.thieme-connect.com/products/ejournals/html/10.1055/a-1061-3205
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	<p>5. Page 6/10, lines 6/10. The Authors correctly discuss that currently used ultrasonographic criteria are of limited diagnostic value for the detection of abnormal cerebral venous drainage. They should mention other diagnostic modalities (they are described thoroughly at: https://pubmed.ncbi.nlm.nih.gov/25255703/)</p> <p>6. Lastly, the Authors should mention possible pathophysiological link between abnormal cerebral venous drainage and multiple sclerosis and also other neurological disorders. It has already been suggested that this potential link regards compromised functioning of the glymphatic system of the brain in the settings of abnormal venous outflow. For reference see: https://pubmed.ncbi.nlm.nih.gov/24344742/ https://pubmed.ncbi.nlm.nih.gov/31526984/</p>
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REVIEWER	Ostengaard, Lasse University of Southern Denmark
REVIEW RETURNED	24-Feb-2023

GENERAL COMMENTS	<p>Comments to the review entitled: "Relevance between chronic cerebrospinal venous insufficiency and multiple sclerosis: a systematic review and meta-analysis".</p> <p>Please attach the protocol as an appendix when it's not available in PROSPERO. Then it would be possible for readers to assess whether the protocol has been followed adequately.</p> <p>The authors use Cochrane's Risk of Bias tool (which is intended for evaluating the risk of bias in randomized trials). However, the included studies are not randomized trials. Could the authors elaborate on why this tool has been used and how 75% of the studies have scored low risk of bias on the item with "Random sequence generation".</p> <p>The authors state that the review was based on PRISMA. Please make sure to report the review in accordance with PRISMA. For example: Item 7 in the PRISMA statement states "Present the full search strategies for all databases, registers and websites, including any filters and limits used". At the moment it is not possible to identify how the search has been conducted in MEDLINE and Embase (Ovid). Please present the full search strategy.</p> <p>Please explain why the authors search for terms like "Multiple Sclerosis," and "multiple adj sclerosis,". The two search terms are technically the same when the search is conducted in MEDLINE and Embase (Ovid).</p> <p>The search is limited to MEDLINE, Embase and citation searches (back/forth) - and a search for gray literature is not described. Please discuss the study's own methodological limitations in regards to the search strategy. For example, could the search strategy have missed relevant studies?</p> <p>Normally, the search strategy will be developed in collaboration with the co-authors and perhaps an information specialist. After this will one person run the search in the databases. The authors have written that "Two authors independently searched the Medline versus Embase databases...". Please elaborate on what this means.</p>
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REVIEWER	Tsivgoulis, Georgios
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	University of Athens, School of Medicine, Athens, Greece
REVIEW RETURNED	01-Mar-2023

GENERAL COMMENTS	The authors have adequately addressed my comments. I am looking forward to seeing this manuscript in print.
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REVIEWER	Capuano, Ana Rush University
REVIEW RETURNED	01-Mar-2023

GENERAL COMMENTS	<p>This is an interesting review of an important topic.</p> <ol style="list-style-type: none"> 1. The outcomes need to be clearly described. For example, "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." Please rewrite this first stating clearly what is the outcome to what the odds ratios were calculated. 2. Please add references (e.g. Cochrane for "I2 values of at least 50% are usually considered to represent substantial heterogeneity, while values of at least 75% indicate considerable heterogeneity.") 3. "Fill and Trim methods were used to correct for publication bias" <ol style="list-style-type: none"> a. The Fill and Trim methods are useful to detect bias, but the correction can still be too liberal. b. Please review the literature. Use this method in conjunction with other publication bias methods, for example more sophisticated selection methods (e.g. Citkovicz and Vevea 2017) 4. Please add the discussion on how accumulation bias was addressed. 5. The methods are not described sufficiently to allow the study to be repeated. <ol style="list-style-type: none"> a. "The pooled ORs for this study were derived using a random-effects model." Please provide more details on the model selected and references. Indicate how model assumptions were verified. b. For the sensitivity analysis please describe the steps of the analysis. Under results instead of stating "Sensitivity analysis of the 20 included papers was applied using STATA 17.0." omit the statistical package and give a brief reminder of what was done. 6. OR not correlation, please describe statistics carefully.
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

Comment 1

Title. From grammatical point of view the phrase "relevance between..." is incorrect. Please change it to "Association between chronic....".

Response 1

Thank you for your comment. We changed "relevance" in the title to "association" and rechecked the grammar (Manuscript, p. 1, lines 1).

Comment 2

For the reader of this paper who is not familiar with this particular topic it would be still unclear what does actually mean the term CCSVI. Moreover, there is a common misunderstanding in the literature regarding this issue.

It should be clearly stated that, for example: "Chronic cerebrospinal venous insufficiency

(CCSVI) is a syndrome characterized by stenoses in the extracranial veins draining the brain, which results in compromised cerebral venous drainage”

For reference see:

https://d1wqtxts1xzle7.cloudfront.net/67179674/The_chronic_cerebrospinal_venous_insuffi20210505-19608-5oz99e.pdf?1620229394=&response-content-disposition=inline%3B+filename%3DThe_chronic_cerebrospinal_venous_insuffi.pdf&Expires=1677233948&Signature=aB6AWq3RQ7ohDhOhnhx5tpWz-ytlS95qLqN2xS4NbPXWQ2e4BPh2cx0lx1CkVB2MuJQOVTaUK6uFqxTDW~aZYF3-UBvYPQz22t4iGk22y0cMcHQKZglxp7nFaQQJXog5YeCmHgGgbdvKkOsEy2l6A8-7C1KOi1v9kZypaIQKD4C61lnCZPQmtnYSp1tj5Cvj~GHBZ4jUsp4YHI8Lxpg3~vCeg7v7KxHeU8~W1~FKuKx~VDV50a0rHNpsnK6FdXwwSJKXV~N67EvoJE4ZbN59v1sU0kQm6Z5axO~LYNRH2S~nly7VNYW5KTmA9CrNsUyyGZmmiXPABsrHk8H0urEDQ__&Key-Pair-Id=APKAJLOHF5GGSLRBV4ZA

Such an abnormal venous drainage can be diagnosed, for example by means of Doppler ultrasound, and hence the so-called Zamboni's criteria represent the most widely used mode of detection. Yet, it can also be diagnosed using MR imaging, cerebral perfusion studies, and catheter venography (which is the most reliable diagnostic method, although invasive one: M Simka, et al.: Catheter venography for the assessment of internal jugular veins and azygous vein: Position statement by expert panel of the International Society for Neurovascular Disease. *Vasa* 2013; 42(3):168-176.).

Response 2

Thank you for your comment. For the readers to better understand the term "CCSVI", we have added a specific explanation of the term in the introduction section and described the diagnostic approach for CCSVI. (Manuscript, p. 2, lines 40–42, and lines 45–48).

Comment 3

Page 2/10, line 44. There should be probably “azygous vein” (no such thing as “odd vein” exists).

Response 3

Thank you for your comment. We have changed "odd vein" to "azygous vein" (Manuscript, p. 2, lines 44).

Comment 4

Page 2/10, line 61. Only one clinical trial on invasive treatment is cited and discussed. Actually, there were several such trials and overview of them has been published at: <https://www.thieme-connect.com/products/ejournals/html/10.1055/a-1061-3205>

Response 4

Thank you for your comment. We have reworked the description of clinical trials of invasive treatments in the introduction section and cited four studies (Manuscript, p. 2, lines 60-62).

Comment 5

Page 6/10, lines 6/10. The Authors correctly discuss that currently used ultrasonographic criteria are of limited diagnostic value for the detection of abnormal cerebral venous drainage. They should mention other diagnostic modalities (they are described thoroughly at:

<https://pubmed.ncbi.nlm.nih.gov/25255703/>.

Response 5

Thank you for your comment. We have added diagnostic modalities other than ultrasonography for abnormal cerebral venous drainage to the discussion section. In addition, we have added a discussion of the multimodal diagnostic approach proposed by the International Society for Neurovascular Disease. (Manuscript, p. 6, lines 206-210).

Comment 6

Lastly, the Authors should mention possible pathophysiological link between abnormal cerebral venous drainage and multiple sclerosis and also other neurological disorders. It has already been suggested that this potential link regards compromised functioning of the glymphatic system of the brain in the settings of abnormal venous outflow. For reference see: <https://pubmed.ncbi.nlm.nih.gov/24344742/>
<https://pubmed.ncbi.nlm.nih.gov/31526984/>

Response 6

Thank you for your comment. We have added a description of the possible pathophysiological link between abnormal cerebral venous drainage and multiple sclerosis and other neurological disorders to the discussion section (Manuscript, p. 6, lines 211-214).

Reviewer 2:

Comment 1

Please attach the protocol as an appendix when it's not available in PROSPERO. Then it would be possible for readers to assess whether the protocol has been followed adequately.

Response 1

Thank you for your comment. During our response to this email, we checked that the PROSPERO status of this study still shows no registration yet. Therefore, we have included the PROSPERO protocol for this study in the supplemental material so that readers can check that we are fully compliant with the protocol (Supplementary Material (PROSPERO)).

Comment 2

The authors use Cochrane's Risk of Bias tool (which is intended for evaluating the risk of bias in randomized trials). However, the included studies are not randomized trials. Could the authors elaborate on why this tool has been used and how 75% of the studies have scored low risk of bias on the item with "Random sequence generation".

Response 2

Thank you for your comment. Many thanks to the reviewers for pointing out our errors in the risk of bias assessment. We made an error in assessing the types of studies included. We explored this further after re-reviewing the included studies, which were observational studies. Because Cochrane's Risk of Bias tool is applied to assess the risk of bias in randomized controlled studies, it does not apply to the articles included. In addition, we have used the NOS scale in our research to assess the quality of the included studies. We decided to remove the content about Cochrane's Risk of bias tool without affecting the content of the study.

Comment 3

The authors state that the review was based on PRISMA.

Please make sure to report the review in accordance with PRISMA. For example: Item 7 in the PRISMA statement states "Present the full search strategies for all databases, registers and websites, including any filters and limits used". At the moment it is not possible to identify how the search has been conducted in MEDLINE and Embase (Ovid). Please present the full search strategy.

Response 3

Thank you for your comment. The full search strategy and database are available in Supplementary Appendix 1 (Supplementary Material, p. 1-2).

Comment 4

Please explain why the authors search for terms like "Multiple Sclerosis," and "multiple adj sclerosis,". The two search terms are technically the same when the search is conducted in MEDLINE and Embase (Ovid).

Response 4

Thank you for your comment. "ADJ" belongs to the location operator retrieved in the OVID database. Its meaning indicates the interval between two search terms. I apologize for any misunderstanding of the reviewer because of the search terms in the manuscript. The specific search terms should be "multiple sclerosis" and "(multiple adj sclerosis).mp.". We have reworked the methods section (Main Document, p. 2, lines 71-72), and the full search strategy has been included in the supplemental file (Supplementary Material, p. 1-2).

Comment 5

The search is limited to MEDLINE, Embase and citation searches (back/forth) - and a search for gray literature is not described. Please discuss the study's own methodological limitations in regards to the search strategy. For example, could the search strategy have missed relevant studies?

Response 5

Thanks for the question. The restrictions put on this research by only searching two databases are covered in the limitations section (Manuscript, p. 6, lines 232-233).

Comment 6

Normally, the search strategy will be developed in collaboration with the co-authors and perhaps an information specialist. After this will one person run the search in the databases. The authors have written that "Two authors independently searched the Medline versus Embase databases...". Please elaborate on what this means.

Response 6

Thank you for your comment. In order to improve the accuracy of the retrieved literature, two authors conducted independent searches of the database in this part of the search, and sought third-party solutions in the parts where opinions differed. We apologize for not being clear in our description and causing reviewers to misunderstand. We have revised this section and added a description of third-party reviewers resolving disagreements to make it easier for readers to understand (Manuscript, p. 2, lines 72-73).

Reviewer 3

Reviewer 4:

Comment 1

The outcomes need to be clearly described. For example, "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." Please rewrite this first stating clearly what is the outcome to what the odds ratios were calculated.

Response 1

Thank you for your comment. An OR > 1 means that the factor is a risk factor for the disease (DOI: <https://doi.org/10.4088/jcp.15f10150>). We originally wanted to express that CCSVI may be a potential risk factor for MS when the OR > 1 . I am sorry that the reviewers misunderstood because of our inadequate description. We have reworked the description of OR (Manuscript, p. 3, lines 103-104).

Comment 2

Please add references (e.g. Cochrane for "I2 values of at least 50% are usually considered to represent substantial heterogeneity, while values of at least 75% indicate considerable heterogeneity.")

Response 2

Thank you for your comment. We have added missing references in the manuscript (Manuscript, p. 3, lines 106).

Comment 3

"Fill and Trim methods were used to correct for publication bias"

a. The Fill and Trim methods are useful to detect bias, but the correction can still be too liberal.

b. Please review the literature. Use this method in conjunction with other publication bias methods, for example more sophisticated selection methods (e.g. Citkowitz and Vevea 2017)

Response 3a

Thank you for your comment. We agreed with the reviewers that "correction" was too liberal, so we have reworked the phrase in the manuscript (Manuscript, p. 3, lines 108).

Response 3b

Thank you for your comment. We agree with the reviewers' recommendation to use this approach in conjunction with other publication bias methods. However, in this study, the Egger's test showed no significant publication bias ($p = 0.241$). Therefore, no further use of the fill and trim methods, let alone in combination with other publication bias methods, was needed in this study. It is possible that the reviewers misunderstood the study because we did not describe it clearly in the section on statistical analyses. We apologize for this. We have reworked the description of publication bias and fill and trim methods in the statistical analyses section (Manuscript, p. 3, lines 107-108).

Comment 4

Please add the discussion on how accumulation bias was addressed.

Response 4

Thank you very much for suggesting that we discuss accumulation bias. We agree with your point of view. However, it is worth noting that accumulation bias cannot be eliminated because subsequent

studies will always be inspired or influenced by previous studies, especially for meta-analyses that add new studies and are continuously updated. (DOI: <https://doi.org/10.12688/f1000research.19375.1>) We attempted to eliminate the influence of previous trials in the subgroup analysis (removing all studies involving Zamboni's team, as Zamboni's team named CCSVI), but the results were not satisfactory. Before this study was written, four meta-analyses discussed the correlation between CCSVI and MS, but only one gave a definite conclusion. There is no doubt that later studies were more or less influenced by previous studies' clinical significance or conclusions, and accumulation bias is unlikely to be avoided. However, these four studies also did not discuss the implications of accumulation bias. Therefore, we added a discussion of accumulation bias to the Discussion section (Manuscript, p. 3, lines 106-107). This section is also intended to provide a framework for subsequent clinical trials that should be aware of the presence of accumulation bias. Although accumulation bias cannot be avoided, the likelihood ratio is an effective means of error control. (DOI: <https://doi.org/10.12688/f1000research.19375.1>)

Comment 5

The methods are not described sufficiently to allow the study to be repeated.

- "The pooled ORs for this study were derived using a random-effects model." Please provide more details on the model selected and references. Indicate how model assumptions were verified.
- For the sensitivity analysis please describe the steps of the analysis. Under results instead of stating "Sensitivity analysis of the 20 included papers was applied using STATA 17.0." omit the statistical package and give a brief reminder of what was done.

Response 5a

Thank you for your comment. We added to the manuscript a description of the choice of fixed or random effects models and the use of random effects models for meta-analysis when heterogeneity is significant (Manuscript, p. 3, lines 101-103).

Response 5b

Thank you for your comment. We removed unnecessary content and reworked the description of the sensitivity analysis results as suggested (Manuscript, p. 5, lines 164).

Comment 6

OR not correlation, please describe statistics carefully.

Response 6

Thank you for your comment. It is possible that we did not describe the meaning of OR clearly in our statistical analysis and the reviewers misunderstood it. We apologize for this. We originally wanted to express that CCSVI may be a potential risk factor for MS when the OR > 1. We have reworked the interpretation of OR (Manuscript, p. 3, lines 103-104).

We thank you for the critical and helpful suggestions. We have taken all these comments and suggestions into account, and have made corrections in this revised manuscript.

We are responding to the criticisms of previous reviewers as you requested. We hope that the revised manuscript is now acceptable for publication in your journal. Thank you again for your consideration.

VERSION 2 – REVIEW

REVIEWER	Simka, Marian University of Opole, Department of Anatomy
REVIEW RETURNED	02-May-2023
GENERAL COMMENTS	paper can be accepted
REVIEWER	Capuano, Ana Rush University
REVIEW RETURNED	Thanks for addressing my previous comments. I have just one last comment. The authors now state that "If the results indicated the

	presence of publication bias, the fill and trim methods were used to detect publication bias." If the method was not used, then omit it from statistics. In publications, one wants to mention what was used and why. It is different from a study plan for example. You can mention that as bias was not detected, estimation and adjustment for bias were not needed.
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VERSION 2 – AUTHOR RESPONSE

Response to Reviewers 4

Comment 1

Thanks for addressing my previous comments. I have just one last comment. The authors now state that "If the results indicated the presence of publication bias, the fill and trim methods were used to detect publication bias." If the method was not used, then omit it from statistics. In publications, one wants to mention what was used and why. It is different from a study plan for example. You can mention that as bias was not detected, estimation and adjustment for bias were not needed.

Response 1

We thank the reviewers for their suggestive and insightful comments. We very much agree with your suggestion and have added a description of the method. The specific description is as follows: "Therefore, there is no need to use the fill and trim methods for further analysis. " [Manuscript (clean copy), p. 5, lines 164]] We hope these answers address your concerns.