PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Early screening for post-stroke depression, and the effect on functional outcomes, quality of life and mortality: a protocol for a systematic review and meta-analysis
AUTHORS	Selvaraj, Sudhakar; Arora, Teresa; Montiel, Tahani; Grey, Ian; Alfraih, Hind; Fadipe, Melissa; Suchting, Robert; Savitz, Sean; Sanner Beauchamp, Jennifer; Östlundh, Linda

VERSION 1 – REVIEW

REVIEWER	Roever, Leonardo Federal University of Uberlândia, Brazil, Clinical Research - Cardiology
REVIEW RETURNED	02-Apr-2021

GENERAL COMMENTS	The purpose of our review protocol is to update and synthesize the currently available literature regarding the associations between timing and setting of PSD screening and mortality, QOL, as well as functional outcomes in stroke survivors. Include in the article: 1 - The diagnostic criteria of the stroke, age of the patients, first or recurrence of stroke .... 2 - Data items 3 - Primary outcomes 4 - Clinical outcomes 5 - Quality of life measures 6 - Assessment of heterogeneity 7 - Subgroup analyzes 8 - Sensitivity analyzes 9 - Meta-regression, 10 - Discussion

REVIEWER	Sarfo, Fred Kwame Nkrumah University of Science and Technology, Neurology Unit, Department of Medicine
REVIEW RETURNED	05-Apr-2021

GENERAL COMMENTS	Comment: It's not clear to me why authors chose to exclude randomized clinical trials and retrospective studies. I would have thought that RCTs would provide excellent data assessing the effect of early screening of PSD on post-stroke outcomes such as quality of life, functional outcomes and mortality. Again, well conducted

| | retrospective studies may have data that could help in answering the research question.

Aside this concern, i think the protocol is generally well written. Thanks |

| REVIEWER | Jehu, Deborah
The University of British Columbia, Physical Therapy |
| REVIEW RETURNED | 14-Apr-2021 |

| GENERAL COMMENTS | Comments to the authors
This systematic review protocol aims to examine the relationship between early screening for post-stroke depression and functional outcomes, quality of life, and mortality. I am confident that this work is novel and will be important to the field. However, the main concern I have is that the authors did not provide enough detail on the measures of interest in multiple sections (e.g., aims, extraction, analysis). Please see below for more details on recommendations for improvement.

Abstract
• Please be specific about which rob assessment you will perform

Introduction
• There is a typo on pg 8 line 29
• Please check the grammar of the research aims. If they are in the form of a research question, please use a question mark at the end of the sentence.
• For aim 1 what do the authors mean that early screening for PSD affects short- and long-term outcome of stoke? Do you mean subsequent strokes? What do you mean by short and long-term? Please define.

Methods
• Meta-analysis (Meader et al., 2013) suggests that the CES-D, HDRS and PHQ-9 are the most promising options to screen for post-stroke depression. While I do see that you have included the PHQ-9 in your search, why did you not include CES-D or HDRS? Additionally, these measures should be explicitly stated in your methods. (MeaderN,Moe-ByrneT, LlewellynA,MitchellAJ.Screeningforpoststrokemajordepression: a meta-analysisof diagnosticvaliditystudies.J NeurolNeurosurg Psychiatry2013.)
• Pg 10 line 39. Please define what you mean by short and long term.
• I suggest that the eligibility criteria are in paragraph form.
• Pg 10 ln 49, please describe how stoke diagnosis will be defined. From medical records, self report, dr diagnosis?
• Given that you already mentioned the study design type that you will include, it is not necessary to write every other study design not to be included in the exclusion criteria.
• For your search, I recommend doing a grey literature search of the reference lists of similar reviews as well as checking either google scholar or web of science for studies that cite your included studies.
• For your search strategy, please indicate the number of hits for each line as well as the final total number of articles for each database. It would be helpful to include different lines so that it's easier to determine which terms were "ORed" and "ANDed" |

• Please be more specific about which measures you plan to extract in term of descriptive (eg age, sex, number of participants) as well as outcome measures (eg mean?, SD?, OR? of which depression screening tools in relation to which functional outcomes, quality of life, and mortality)
• Please be more specific that the Newcastle Ottawa Scale is assessing the risk of bias. Assessing the quality of reporting is different, and the authors may also consider this for their review.

Data analyses
The data analyses appear to be rigorous. Please be very specific about which measures you will include in the meta analysis, as opposed to indicating "an outcome of interest". How many studies are necessary to be included in the meta analysis? Will you be doing any sensitivity analyses, such as for the severity of baseline stroke or type of stroke? Please clarify.

REVIEWER	Hinwood, Madeleine
	The University of Newcastle, School of Medicine and Public Health
REVIEW RETURNED	18-Apr-2021

| GENERAL COMMENTS | The authors present a protocol for a systematic review and meta analysis on the association between early screening for post-stroke depression and outcomes including stroke recurrence, quality of life, and mortality. The protocol is sound overall, uses of available check-lists and complies with relevant guidelines. The review design overall seems robust and investigates an important area of stroke recovery. I look forward to reading the final review. I just have a few comments:

Throughout paper:
The manuscript would benefit from a thorough read-through and revision with emphasis on accuracy and grammar. There are a few minor errors throughout. For example, although the abstract states that the review has been submitted to PROSPERO, the main body states it is registered.

Abstract:
In the introduction, the direction of the effect between post stroke depression and outcomes should be stated.

Introduction:
Aim 2 should be re-worded
The rationale for the study could be improved, particularly with reference to previous literature/other reviews in similar fields. Why is this review important to conduct?

Search strategy:
How was (or will be) the search strategy developed? If developed based on other published systematic searches, this should be acknowledged. Updating the search prior to review submission to ensure study information is as up to date as possible may also be a worthwhile step to include.

Inclusion criteria:
Is there a minimum duration of follow up you would include?

Data extraction:
There may be additional variables to extract other than those listed here, particularly around stroke severity and other potential |

| | confounders, and length of follow up. You could include a line stating that data extraction forms will be piloted on a small number of articles and adjusted as necessary.

Data analysis:
Will you perform any adjustment for confounders? For example, differences between study populations, length of follow up, etc? If so this could be acknowledged.

Strengths and limitations:
These could be revised to focus on the strengths and limitations of the design of the review and meta-analysis in particular, not to the expected results. For example, the strengths of the manuscript include the study design, and compliance with relevant guidelines for systematic reviews. |
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VERSION 1 – AUTHOR RESPONSE

Comments from reviewers

Reviewer 1: Dr. Leonardo Roever, Federal University of Uberlândia, Brazil

- Comments to the Author:
The purpose of our review protocol is to update and synthesize the currently available literature regarding the associations between timing and setting of PSD screening and mortality, QOL, as well as functional outcomes in stroke survivors. Include in the article:
1 - The diagnostic criteria of the stroke, age of the patients, first or recurrence of stroke ....
2 - Data items
3 - Primary outcomes
4 - Clinical outcomes
5 - Quality of life measures
6 - Assessment of heterogeneity
7 - Subgroup analyzes
8 - Sensitivity analyzes
9 - Meta-regression,
10 - Discussion

Authors' response:
We have addressed the reviewers' suggestions in the manuscript and organized the subtitles as suggested for better clarity.

We applied the World Health Organization (WHO) definition of stroke and included all patient age groups with acute onset stroke.

Reviewer: 2, Dr. Fred Sarfo, Kwame Nkrumah University of Science and Technology

- Comments to the Author: It's not clear to me why authors chose to exclude randomized clinical trials and retrospective studies. I would have thought that RCTs would provide excellent data assessing the effect of early screening of PSD on post-stroke outcomes such as quality of life, functional outcomes and mortality. Again, well conducted retrospective studies may have data that could help in answering the research question.
Aside this concern, i think the protocol is generally well written. Thanks

Authors' response:
We thank the reviewer for the suggestion. We focused on naturalistic studies however we carefully considered the option of including RCTs. However, when we evaluated our pilot searches, we found that the range of interventions studied in RCTs was extremely variable and also, controlling for outcomes were difficult. Furthermore, RCTs are typically shorter time-framed and therefore confounds our aim investigating the early depression screening and its impact on long term stroke outcome. We excluded retrospective studies, due to bias associated with the studies, selection and recall bias, and also difficulties in ascertaining temporal relationships between depression and stroke outcomes. We have now included this information within the strengths and limitations section of our revised article.

Reviewer: 3: Dr. Deborah Jehu, The University of British Columbia

- Comments to the Author: This systematic review protocol aims to examine the relationship between early screening for post-stroke depression and functional outcomes, quality of life, and mortality. I am confident that this work is novel and will be important to the field. However, the main concern I have is that the authors did not provide enough detail on the measures of interest in multiple sections (e.g., aims, extraction, analysis). Please see below for more details on recommendations for improvement.

- Abstract: Please be specific about which rob assessment you will perform

Authors' response:
We thank the reviewer for identifying the lack of specification of a risk of bias (ROB) tool in the abstract. The Newcastle Ottawa Scale will be used and has now been specified in the abstract as well as the main article.

- Introduction
• There is a typo on pg 8 line 29
• Please check the grammar of the research aims. If they are in the form of a research question, please use a question mark at the end of the sentence.
• For aim 1 what do the authors mean that early screening for PSD affects short- and long-term outcome of stoke? Do you mean subsequent strokes? What do you mean by short and long-term? Please define.

Authors' response:
We apologize for this oversight. We have checked and corrected the typos and grammar throughout the text. Our primary objectives were to investigate if hospital screening for depression in patients admitted for acute stroke events or within three months of acute stroke affects stroke-related outcomes – mortality, stroke recurrence, stroke-related disability, and quality of life. We defined the short term as within three months of an acute stroke event based on critical recovery and clinical follow up and the long term as at least one year and after 1,2.

Our primary aims for this review are, as follows:

1. To investigate if early post-stroke depression symptoms in hospitalized patients immediately after stroke is associated with worse stroke related disability at short term (within 3 months) after an acute stroke event

2. To investigate if early post-stroke depression (at acute hospital admission or within 3 months) associated with long-term (>1 year) stroke related health outcomes (stroke related disability, stroke recurrence, mortality, quality of life)?

The above two aims have now been documented clearly in the revised article submission.
- Methods Meta-analysis (Meader et al., 2013) suggests that the CES-D, HDRS and PHQ-9 are the most promising options to screen for post-stroke depression. While I do see that you have included the PHQ-9 in your search, why did you not include CES-D or HDRS? Additionally, these measures should be explicitly stated in your methods. (MeaderN,Moe-ByrneT, LlewellynA,MitchellAJ.Screeningforpoststrokemajordepression: a meta-analysisof diagnosticvaliditystudies.J NeurolNeurosurg Psychiatry2013.)

Authors' response:
We thank the reviewer for the suggestion. We agree with the reviewer, and we intend to include all validated questionnaires used in the post stroke depression studies.
- Pg 10 line 39. Please define what you mean by short and long term.
Authors' response: We defined the short term as within three months after an acute stroke event and long-term as at least 1 year or above for the stroke related health outcomes.
- I suggest that the eligibility criteria are in paragraph form.

Authors' response: We have described the eligibility criteria in paragraph.
As requested by the reviewer, we have now presented the inclusion and exclusion criteria in paragraph form.

- Pg 10 ln 49, please describe how stoke diagnosis will be defined. From medical records, self report, dr diagnosis?

Authors' response:
In this review, we will verify the diagnosis by stroke clinicians (WHO/ICD criteria), medical records and also self-report. We will check if the clinical diagnosis of stroke was made as per the World Health Organization (WHO) definition of stroke: "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin". Therefore we will exclude transient ischemic attack (TIA) and stroke symptoms caused by subdural hemorrhage, tumors, poisoning, or trauma3. We will do sensitivity analysis of studies that report self-reported stroke diagnosis.

- Given that you already mentioned the study design type that you will include, it is not necessary to write every other study design not to be included in the exclusion criteria.

Authors' response: The reviewer's point is noted. We wanted to make the inclusion and exclusion criteria very clear and therefore specified all of the study designs.

- For your search, I recommend doing a grey literature search of the reference lists of similar reviews as well as checking either google scholar or web of science for studies that cite your included studies.
Authors' response: We thank the reviewer for the suggestion. A structured screening of the reference lists of all included studies and eventual reviews located in the search will be conducted. Updated information is added to the manuscript.

A comprehensive search in Web of Science (and the other included databases) will be conducted where eventual, relevant cross-cited papers will be included. We have chosen not to include Google Scholar in our search dues to the lack of sufficient search tools needed to apply a structured, systematic search approach and the high inclusion of nonpeer-reviewed and potential predatory materials. Our broad and detailed developed search strategy in the six databases is designed to cover all potential relevant, high-quality papers that can be found indexed in Google Scholar.

Our inclusion criteria are defined as peer reviewed, publish data only. This is also reflected in the search string where search terms for the selected study types are included. We have therefore decided to not cover unpublished and grey sources in this review.

- For your search strategy, please indicate the number of hits for each line as well as the final total number of articles for each database. It would be helpful to include different lines so that it's easier to determine which terms were "ORed" and "ANDed"

Authors' response:
We thank the reviewer for the suggestions to enhance the reporting of the pre-search. The search string has been updated with notes and results for all search units to increase the readability of the search details.

Following the PRISMA-P reporting guidelines, we have presented a draft search only as support for developing the protocol. A full, transparent and reproducible search strategy for all included databases (PubMed, Embase, APA PsycInfo, Scopus, Web of Science and CINAHL) will be provided in the final review. This is now specified in the manuscript

- Please be more specific about which measures you plan to extract in term of descriptive (eg age, sex, number of participants) as well as outcome measures (eg mean?, SD?, OR? of which depression screening tools in relation to which functional outcomes, quality of life, and mortality)

Authors' response:
We will create a template to extract information about study type (prospective clinical and case registry), publication year, population characteristics (country, patient age, sex, total numbers of participants, completed and lost to follow up), mortality, illness characteristics (type of stroke (ischemic or hemorrhage; where possible hemisphere involved), hospital or outpatients data, length of follow-up, Outcome data will include depression scale (validated scales), time of screening for depression, stroke disability ratings, mortality data and quality of life scores. We piloted the data extraction on 5 full text articles and have thus adjusted the variables accordingly.

- Please be more specific that the Newcastle Ottawa Scale is assessing the risk of bias. Assessing the quality of reporting is different, and the authors may also consider this for their review.

Authors' response:
We have added the statement that we will strictly follow PRISMA guidelines for reporting the systematic review. We will use the Newcastle Ottawa Scale for assessing the quality of nonrandomized studies and the risk of bias.

- Data analyses: The data analyses appear to be rigorous. Please be very specific about which measures you will include in the meta-analysis, as opposed to indicating "an outcome of interest". How many studies are necessary to be included in the meta- analysis? Will you be doing any sensitivity analyses, such as for the severity of baseline stroke or type of stroke? Please clarify.

Authors' response:
We have updated the "Data analysis and synthesis" section to describe the exact outcome measures that we will be evaluating and sensitivity analyses (meta-regressions). Outcomes include stroke disability scales (Barthel index; Modified Rankin Scale; Glasgow Coma Scale), Quality of Life (Short Form 36 (SF-36); Stroke-Specific Quality of Life (SS-QOL); Euro Quality of Life (Euro-QOL)), and Mortality (dichotomous). The lower bound of studies to be included in any given meta-analysis is 2 (see Cochrane.org; Valentine et al., 20104); however, our goal is to have as many as meet the inclusion/exclusion criteria. Finally, we will perform meta-regression to account for the influence of

stroke severity (NIH Stroke Severity), type of stroke (ischemic vs. hemorrhagic), and length of follow-up.

Reviewer: 4: Dr. Madeleine Hinwood, The University of Newcastle

- Comments to the Author: The authors present a protocol for a systematic review and meta-analysis on the association between early screening for post-stroke depression and outcomes including stroke recurrence, quality of life, and mortality. The protocol is sound overall, uses of available check-lists and complies with relevant guidelines. The review design overall seems robust and investigates an important area of stroke recovery. I look forward to reading the final review. I just have a few comments: Throughout paper: The manuscript would benefit from a thorough read-through and revision with emphasis on accuracy and grammar. There are a few minor errors throughout. For example, although the abstract states that the review has been submitted to PROSPERO, the main body states it is registered.

Authors' response:
We thank the reviewer for the relevant suggestions. The PROSPERO registration information in the abstract and under "Methods and analysis" is now updated. Our registration is reviewed and accepted in PROSOPERO. - Abstract: In the introduction, the direction of the effect between post stroke depression and outcomes should be stated.

Authors' response:
We have added the following statement. "We hypothesize that patients with early post-stroke depression at hospital or within 3 months, will have a substantial disability, poorer quality of life and increased mortality" - Introduction: Aim 2 should be re-worded The rationale for the study could be improved, particularly with reference to previous literature/other reviews in similar fields. Why is this review important to conduct?

Authors' response:
We have added the texts further explaining the study rationale in the introduction.

- Search strategy: How was (or will be) the search strategy developed? If developed based on other published systematic searches, this should be acknowledged. Updating the search prior to review submission to ensure study information is as up to date as possible may also be a worthwhile step to include.

Authors' response:
We thank the reviewer for this very valid and constructive points. The manuscript has been updated with more details to clearly describe the search process. Information about the planned search update is also added together with practical details for this process (see the sections: "Information sources and search strategy" and "Data management").
The preliminary search strategy in PubMed is developed by a medical librarian specializing in systematic review and meta-analysis methodologies with clinical input from the subject specialists. The search does not build on, or include parts from, earlier published reviews.

- Inclusion criteria: Is there a minimum duration of follow up you would include?

Authors' response:
We selected one year as a minimum duration of post-stroke follow-up.

- Data extraction: There may be additional variables to extract other than those listed here, particularly around stroke severity and other potential confounders, and length of follow up. You could include a

line stating that data extraction forms will be piloted on a small number of articles and adjusted as necessary.

Authors' response:
We thank the reviewer, and this is an excellent point. We have added the following statement in the introduction to strengthen our rationale for the study. We will pilot the data extraction on 5 full-text articles and will adjust the variables accordingly. - Data analysis: Will you perform any adjustment for confounders? For example, differences between study populations, length of follow up, etc? If so this could be acknowledged.

Authors' response:
We will be performing meta-regression to assess the potential influence of stroke severity (NIH Stroke Severity), type of stroke (ischemic vs. hemorrhagic), and duration of follow-up. If notable differences between study populations may be coalesced into distinct categories, meta-regression will evaluate the influence of these as well.

- Strengths and limitations: These could be revised to focus on the strengths and limitations of the design of the review and meta-analysis in particular, not to the expected results. For example, the strengths of the manuscript include the study design, and compliance with relevant guidelines for systematic reviews

Authors' response:
Thanks, this is a good point. We have added a strengths and limitations section within the revised manuscript.

References:
1. Prabhakaran S, Zarahn E, Riley C, et al. Inter-individual variability in the capacity for motor recovery after ischemic stroke. Neurorehabil Neural Repair. 2008;22(1):64-71.
2. Ward NS. Restoring brain function after stroke - bridging the gap between animals and humans. Nat Rev Neurol. 2017;13(4):244-255.
3. Aho K, Harmsen P, Hatano S, Marquardsen J, Smirnov VE, Strasser T. Cerebrovascular disease in the community: results of a WHO collaborative study. Bull World Health Organ. 1980;58(1):113-130.
4. Valentine JC, Pigott TD, Rothstein HR. How Many Studies Do You Need?: A Primer on Statistical Power for Meta-Analysis. Journal of Educational and Behavioral Statistics. 2010;35(2):215-247.

VERSION 2 – REVIEW

REVIEWER	Hinwood, Madeleine
	The University of Newcastle, School of Medicine and Public Health
REVIEW RETURNED	30-Jun-2021

GENERAL COMMENTS	All of my comments have been addressed. Thank you.