Author’s response to reviews

Title: A Systematic Review Protocol of Stigma among Children and Adolescents with Epilepsy

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Author’s response to reviews:

RESPONSE TO REVIEWERS’ COMMENTS.

We thank you for giving us the opportunity to revise this manuscript in light of the reviewer’s comments. We have addressed all the comments point by point; the reviewer’s comments have greatly improved the quality of manuscript.

Reviewer #1:

• P4. Line 1. Please correct "at least"

We have made this correction

• P5, L15: Please consider adding more context about why epilepsy has the Stigma problem. There are historical and cultural factors that explain the reasons for this stigma (I suggest using some of the ideas from: DeBoer HM. Epilepsy 2010; 19(10):630-636)

We thank the reviewer for this comment. We have added and referenced the text about the factors that may explain stigma on page 3 lines 72-75 XXXX

• P1, L39-40: Authors mention that the results from previous studies among patients in HIC and LMIC have been conflicting. How have they been conflicting? Were they reviews? Were they
just cross sectional studies? Is there any systematic reviews combining them or is this the first one? Are you only interested in SSA A brief description of what they found and why we should not trust them, or why this study pretend to resolve that conflict, should be in the background.

We thank the reviewer for this comment, and agree that we were not very clear about this conflicting data. In the background section (Page 3 line 84-90), we highlight this conflict. The majority of the studies were cross-sectional; we were not able to identify a systematic review that synthesized literature about the prevalence of stigma in this population (children and adolescents)

• P1;L52-58: Also, if SSA is you only interest, as it's described in the Objectives, your title and the Aims (P2, L7-10), should reflect that

The review is going to consider all studies conducted globally. The corresponding changes in objectives have been done.

• PROSPERO registration states that this review started in June 2017, and it's expected to finish in February (in less than 2 months), and the PROSPERO stages are checked as if they have not started yet. There should be consistency among the stages and the current dates and the status of this protocol

We thank the reviewer for pointing out this discrepancy. We have since updated the protocol in PROSPERO

• P2, L7-11: Aims should not be included within Methods. It should a subheading before Methods

We have made this correction

• P2, L14-15: What is the meaning of the 1-Superscript along with the (SSA)1? Does not seem to be a citation, which used brackets.

This was a typographical error which has been corrected

• All P2: Trying to make your question fit into a PICO or PECO format is unnecessary and also inappropriate. SR of prevalence questions should have a question that reflects its real aim, not a PICO which is related mostly to interventions/exposures(and sometimes Dx tests). The following paragraph from the Joanna Briggs Institute Manual for SR of Prevalence and Incidence data might be useful:

-Reviews that aim to describe the distribution of existing variables or seek to answer the question "how common is a particular disease or condition in a specific group of individuals?” are often classified as descriptive and will utilize measures of prevalence and incidence to answer such lines of enquiry. The objective of these reviews is to describe the health issue (what), those
affected by it (who) as well as the location (where) and the time period (when) in which the health issue occurred.

We thank the reviewer for this guidance. Appropriate changes have been made in the methods section (pages 3-4, lines 108-120).

• All P2: Also trying to make the Factors associated, fit into secondary outcomes is even more inappropriate. I think that determining factors associated is itself a different question. In addition to that I perceive a third question related to the available interventions. Authors may want to clearly describe this review a 3 questions review

We thank the reviewer for this comment. We have since limited our research question to prevalence of enacted and perceived stigma and associated factors (page 4, lines 116-120). Interventions towards prevention and reduction of epilepsy related stigma is being designed as an independent systematic review. This will enable extensive and detailed reviews for both topics, which are both very sensitive and crucial in the understanding of epilepsy related stigma

• P2, L42-44: Searches through CINAHL should be included. This database include info from some Nursing Journals that may include relevant information for your question. Also, there is no search strategy provided (even though authors stated in the PRISMA checklist it was in lines 224-239, which I could not find)

We have added CINAHL as one of our search engines. The search strategy has also been included (page 4 lines 121-142).

• P2, L48-57: The eligible studies should be linked to each one of the questions this review has.

The eligible studies have been linked to each review question (pages 5 lines 158-164)

• P3, L5: What will authors do if there are multicenter trials including SSA and non-SSA countries? How will they handle that scenario?

We thank the reviewer for raising this important question. Since the review has been changed to focus on studies done worldwide with a specific interest on children and adolescents, all multicenter studies that answer any of the review questions will be included.

• P3, L14-33: There is no clear mention of how the Title and abstract screening will be done. There isn't neither info about the full text screening. There is no info if these steps will be done or note independently and in duplicate. Additionally, authors plan to do the data extraction will be performed by one author and checked by another author. This approach has some limitations and is not the actual recommendation by the Cochrane Collaboration. This approach (one extractor + checking) has shown more errors than duplicate extraction (Buscemi; J Clin
Epidemiol 2006). I suggest to reevaluate this approach and plan a data extraction in duplicate, since this might be an important limitation of this review.

We appreciate the reviewer’s comment, have included a clear and detailed approach of handling data under the “study and data management” (pages 4-5, lines 144-155) and “data extraction” (page 5 lines 166-179) section.

• P3, L36-48: Not clear to me why if they are using a NIH tool, there is need to use RevMan? Risk of Bias should be detailed in tables. No need to use a software designed foe effectiveness meta-analysis.

This has been addressed. Risk of bias will be assessed using Quality In Prognostic Studies (QUIPS) tool (page 6 lines 195-196).

• ALL P3: I found a little bit annoying that many analyses and approaches are not referenced appropriately: No citation for the RoB Tool, No citation for the GRADE approach, no citation of the Egger test. I suggest authors to be cautious with this, since no adequate citations might be considered form of plagiarism.

We have noted this with concern, and have referenced all approaches mentioned (page 6, lines 195-203).

• P3, L53-55. I understand the final measure: Mean prevalence and CI. Not clear the analysis of the stigma associated factors with univariate and logistic regression? To start, this question has not been clearly described from the beginning, and now there is mention of logistic regression: What are the considered, or suspected independent variables? How will authors choose what variables to include in the regression? What will be the software for this analysis?

We have noted these comments, and will limit our analyses to mean prevalence and CI

• P4, L4-7. What will authors do with high heterogeneity?

We will use the forest plot and I2 statistic to assess for heterogeneity, in the event that we find statistically significant heterogeneity, then we will report our results as a narrative. We have included this in our methods section (pages 5-6, lines 185-191)

• P4, L10-12. WhEffect modifiers should not only be mentioned before the analysis, but also an analysis of what potential impact they might have on the effect. Namely, what should be the change in the direction of the effect when these modifiers are present?

Thank you for this comment. We have included this correction in the protocol on page 5-6, line 189-191.
Reviewer #2:

- At present the article is seemingly addressing two distinct research questions and the methodology does not seem to be in synergy with the research questions. See attached report.

We thank the reviewer for critically looking at the protocol and pointing this out flaw. The comments raised in the specific sections have been addressed, and we are confident that addressing them has improved the quality of this manuscript.

Background

- Line 15 – it’s important for authors to define terms … enacted and perceived stigma. Not all prospective readers will be familiar with these terms, yet they are the core concepts of the manuscript.

These terms have been defined and referenced on page 3 lines 77-80.

- Lines 15-21 “The presence of stigma among children and adolescents has been associated with low self-esteem, a poor quality of life, retardation in neuro-cognitive development, and academic progress [9]– [11]. Stigma among patients with epilepsy has also been associated with poor health seeking behaviours, and increased rates of mortality (mainly through suicide) [12], [13].” Could be merge into a single, compound sentence as the concepts are essentially the same. Authors are especially encouraged to write concisely.

The sentences have been merged (page 3 lines 80-83).

- Lines 29-30: “Whereas some literature indicates that the above factors associated with stigma of epilepsy, several other studies have not documented such association [16].” This is a very important point and needs to be fully expanded. Authors need to criticize the cited articles and briefly explain the discrepancies between the studies.

This discrepancy has been well expounded and all cited articles have been critiqued accordingly (page 3 lines 93-97).

- Lines 31- 32; “Additionally, negative explanatory models of the condition…”- this statement is not very clear, what do you mean by this?

This refers to the negative misconceptions people have about epilepsy which contribute towards its stigma as explained on page 3 lines 97-100

- Lines 34 – 40: A number of studies have been done to determine the prevalence of epilepsy related stigma in high-income countries (HIC) [18] and low and middle-income countries (LMIC) including sub-Saharan Africa (SSA) [14], [19]. However, findings from these studies have been conflicting with very high variations.”
Firstly, authors need to provide full context so that prospective readers can critique the evidence provided for instance, it’s worthwhile to cite the actual incidences to demonstrate the magnitude of the problem and perhaps provide evidence for the need of a systematic review on factors associated with stigma.

All the necessary incidences and prevalences have been cited in the background (page 3 lines 84-87)

The statement “However, findings from these studies have been conflicting with very high variations” needs to be rephrased as it is not very clear

Has been addressed

What are the reasons for the “...high variations”? this needs to critically appraised as this forms a huge basis for the study e.g. could the variations be due to differences in methodologies or operational definitions?

The cause for variations critically appraised as indicated page 3 lines 87-90.

“… makes the extrapolation of findings from HIC to SSA inappropriate” I think this text is out of context as authors earlier on cited that some of the studies were done in SSA. Authors are advised to be consistent in their argument.

The study scope has been changed to include all studies worldwide to enable us compare and contrast the different geographical locations.

• The first aim is double-barrelled and therefore not succulent

Thank you for raising this up. Indeed the aim needs to be succinct; we have since rephrased to read “To determine the prevalence of enacted and perceived stigma of epilepsy among children and adolescents with epilepsy”.

• “To document the various available interventions aimed towards reduction of stigma of epilepsy among children and adolescents with epilepsy globally.” I think authors need to take the systematic review a notch further and critically appraise the level of evidence of the available interventions. It’s not good enough to just identify interventions, issues such as acceptability, feasibility, efficacy among other issues need to be appraised if the goal of the systematic review is to ultimately work towards the eradication of stigma in epilepsy as authors argue. I think that the review is focusing on two distinct research questions, which could warrant two separate systematic review. This is even reflected in the methods section, the way the PICO are outlined is just confusing.
We appreciate this concern and will limit the review to “prevalence of stigma and its associated factors among children and adolescents with epilepsy”

- These findings will be used in guiding policy makers to allocate funds to effective interventions that tackle the burden stigma in epilepsy. - this point is a “bit far-fetched” as nowhere in the background was there a mentioning of the relationship between stigma and policy!

This statement has been rephrased to ‘findings will be used in enlightening researchers, clinicians and policy makers about the burden of stigma among patients with epilepsy in SSA. Appropriate interventions can be instiutied based on these findings

Methods

- There is no synergy between aims and the methodology

We acknowledge that this is very important and we have harmonized our methodology to achieve the aim.

- There is need to justify inclusion of only cross-sectional surveys investigating various interventions

We agree that the justification for including the studies was not clear. By limiting our research question to an assessment of the prevalence of stigma in epilepsy, we have been able to address this concern. The kind of studies that would answer this question would ordinarily be cross sectional in nature. .

- Please use initials only under data extraction process, authors” full names should be provided as per author instructions

This has been taken into consideration on pages XXX

- Please provide more information on the risk of bias assessment tool e.g. its psychometrics

Risk of bias will be assessed using Quality In Prognostic Studies (QUIPS) and more information been provided with a reference (page 6, line 195-199).

- What do you mean by this? “The methodological quality of the review will be assessed using Review Manager (RevMan) 5.3.5 at all stages of study and two independent people from the team will carry this out.”

This has been reviewed and omitted. Methodological quality of the studies will be assessed using Grading of Recommendations Assessment, Development and Evaluations (GRADE) approach as shown on page 6 line 202-203.
• “Studies involving assessment of prevalence of stigma will be assessed for the appropriateness of the stigma tools used”. Again, please be more explicit, what psychometric of the tools are you going to evaluate and why?

We are cognizant of the fact that prevalence of stigma could vary based on the instruments used. In order to address this concern, we will document the types of tools used, their cut off scores and their psychometric properties (page 6 lines 200-201).

• “Publication bias will be assessed using funnel plot and Egger regression test.” – do you expect the methodologies to be homogeneous? Again, this directly contradicts information provided in the background section. This also applies to the proposed meta-analysis.

We appreciate this comment and we have harmonized this in the methodology section (page 5-6, lines 185-192) to match the information in the background. A meta-analysis will only be conducted if there is data from the studies is homogeneous.

Minor comments

• Punctuation error for words at least – line 8

We have addressed this

• Page numbering will make the manuscript much easier to review

We have taken note, and addressed this Authors are also encouraged to format the article in accordance with the journal guidelines e.g. [6]–[8] ought to have been cited as [6-8].

Noted and necessary changes made.

• Related stigma should be written as a single word i.e. related-stigma

Addressed and all the necessary changes have been made.

• Please avoid use of the word “vice”

Addressed and necessary changes made.

Associate Editors Comments:
Thank you for your submission. The two reviewers have provided considerable guidance for editing this manuscript so it could meet the requirements of our journal. I echo it requires substantial work but it is an interesting topic and I hope you find the feedback helpful for your next stage. Please see some further comments I have below:

Thank you for the comments and recommendations made. They were all very helpful and have made a significant improvement in our protocol.

Background

- P5 of line 8. States its ‘highly prevalent among children’ – how much? Can a figure be quoted?
Figures have been quoted as shown on page 3 lines 84-87.
- P5 line 29. Sentence doesn’t flow. Suggest you remove ‘that’ to read ‘Whereas some literature indicates the above factors’
We have addressed this.
- P6 line 36/37 – Children can be with a lower case c ‘Factors associated with stigma of epilepsy among children
We have addressed this.
- Searches (p6 line 42-46) - will Google scholar look for grey literature? Start dates of searches?
Yes, google scholar will look for grey literature starting from the date of inception of the database up to the time of the literature search for this review (page 4, lines 123-124).
- P7 line 18/19. Please add a space before the name Amir Abdallah
We have addressed this (page 5, line 149).
- P7 line 22/23. Please add ‘a’ to read ‘Data will be extracted using a pre-piloted’
We have addressed (page 5 line167)
- P7 line 57/58 . Suggest ‘Factor’ is made plural i.e. ‘Factors associated with stigma of epilepsy’
Missing full stops at the end of some paragraphs e.g at the end of the Risk of Bias paragraph and Strategy for data synthesis paragraph. Please check manuscript throughout and add full stops were appropriate.
We took note of this and necessary changes have been made throughout the protocol.
• P8 – search strings are not a reproducible search strategy

A search strategy has been provided on page 4, lines 121-142

• P9  The diagram labelled ‘search strategy’ is not a search strategy, it is a PRISMA study flow diagram. It is not needed until the review is complete and you have numbers articles for each of the boxes. A Search strategy is the search terms (words, phrases, index terms..) and the syntax used to combine them when searching a database. It should be presented so it is fully reproducible, i.e. the reader can achieve the same search results as the author because they can see exactly how to enter the terms into the database. See the searches in Tables 2 and 3 in this recent protocol as an example https://systematicreviewsjournal.biomedcentral.com/articles/10.1186/s13643-018-0679-8

We noticed this and made all the necessary changes. A new search strategy has been provided. Thank you for the resource material which was very helpful.

• A couple of papers looked relevant to include in your background section. See: Levira F, Thurman DJ, Sander JW, Hauser WA, Hesdorffer DC, Masanja H, Odermatt P, Logroscino G, Newton CR. Premature mortality of epilepsy in low-and middle-income countries: A systematic review from the Mortality Task Force of the International League Against Epilepsy. Epilepsia. 2017 Jan 1;58(1):6-16.


Please also take a moment to check our website at https://sysr.editorialmanager.com/l.asp?i=46520&l=363OE03K for any additional comments that were saved as attachments. Please note that as Systematic Reviews has a policy of open peer review, you will be able to see the names of the reviewers.

Thank you for all the resources provided. They have been very useful guides in improving our protocol.